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WO 02/070464 A2

(54) Title: NOVEL HYDRAZONES

(57) Abstract: The •v... relates to novel h ydraz.e deriva.ves and their use as ac.ve • gredi.ts • the prepara.. of pharmaceutical composi..s. The •v..on also c.cerns related as pects •clud• g processes for the preparati. of the com pounds, pharmaceu.cal com posi..s c.tain• g one or more of those compounds and especially their use as an. •fec.ves.

Novel Hydrazones

The present invention relates to novel hydrazones, in particular to a process for the manufacture of the hydrazones, to pharmaceutical compositions containing them and to their use in the treatment of microbial infections.

Related hydrazones have been previously suggested to have antitumour agents (see Antonini et al., *J. Med. Chem.* **1981**, *24*, 1181-1184. Notably PIH (Pyridoxal Isonicotinoyl Hydrazone) seem to display promoted antiproliferative activity: Richardson, D.R.; Milnes, K. *Blood* **1997**, *89*, 3025-38. Molovac, azaryl and diazinyl hydrazones a potential similarity: Easmon, J.; Heinisch, G.; Pürstinger, G.; Langer, T.; Ostrowicki, J.K.; Grunicke, H.H.; Hofmann, J. *J. Med. Chem.*, **1997**, *40*, 4420-4425. The inhibition of tumor growth seems to be linked to their (III) chelating property: PIH: Richardson, D.R. *Antimicrob. Agents Chemother.* **1997**, *41*, 2061-2063.

So far only few peptides have been discovered to inhibit the bacterial ribosomal protein synthesis (PTS) which is a drug target system useful for identifying new anti-microbials. It has now been found, most of the hydrazones of formula **1** of the present invention are potent inhibitors of enzyme I of the bacterial ribosomal protein synthesis system ("PTS") (cf. experimental table 1). Inhibition of enzyme I is expected to decrease bacterial virulence and pathogenicity, as demonstrated by gene knock-out studies (Eur. Pat. Appl. EP 0 866 075). Consequently, low molecular weight organic compounds affecting this phosphoryl cascade may be useful in the treatment of bacterial infections in human and/or veterinary medicine.

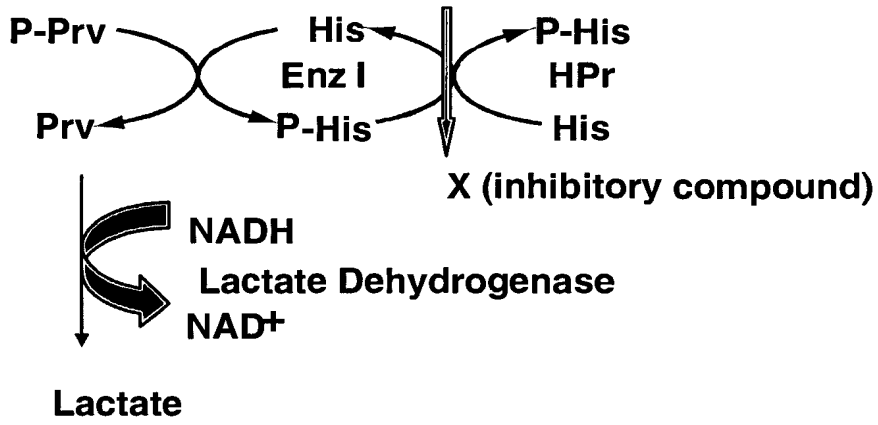
It has also been found that a number of these compounds, although inactive in PTS, exhibit antibacterial activity. Several compounds of formula **1** are very specific in exhibiting antibacterial activity consequently these compounds of formula **1** are generally useful to combat bacterial pathogens in human and

animals, e.g. to combat Gram positive pathogens such as Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis or Streptococcus pneumoniae etc., and Gram negatives like Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae or Proteus vulgaris.

The determination of activity of a compound of the present invention in the PTS may be summarized as follows:

Assay for enzyme I dependent PEP: peptide phosphotransferase activity.

PTS- Inhibition Assay



To find inhibitors of Enzyme I of the PTS by high throughput screening, an *in vitro* assay based on spectrophotometric read out at 340nm has been set up. The assay comprises of three major components, purified enzyme I in catalytic amounts, Phosphoenol Pyruvate (PEP) as the phosphoryl donor substrate and purified HPr as the phosphoryl acceptor substrate.

The assay couples the formation of pyruvate formed from PEP to lactate, catalyzed by lactate dehydrogenase. The disappearance of NADH, cofactor required by lactate dehydrogenase, is determined spectrophotometerically at 340

nm. The assay is d.e , a U-shaped microtiter plate format, and quantitati. is d.e u s, g microplate absorbance la,r.

100 µl l acti. mixt ul c.t a,ed 0.8 mM PEP, 0.2 mM NADH, 3 µg lactate , , .o g. ase (Boehr, ger Mannheim), 50 mM KP_i pH=7.5, 2.5 mM dithiothlitol , 2.5 mM NaF, 5 mM $MgCl_2$, and betwe. 50 and 100 µM of the compound. The l acti. is started by the additi. of .z yme l (f, al conc.tr ati. 0.75 µM). In a c.trol experim.t the compound is l placed by DMSO.

The ls ults obta,ed al s ummarized table 1.

Table1

Compounds	Example	Synthetic method	Inhibiti. of PTS (IC50 , uM)
N'-(2,5-Di, . oxy-benzyl,.e)-b.zo , drazi,	1	A	15
N'-(2-Hy,; y-benzyl, en, -2-(1H-indol-3-,) -aceto, .azi,	2	A	50
N'-(2,5-Di, ,; y-benz, ,.e)-naphthal.e -1-carbo, . azi,	3	A	6
3,4,5-Trimethoxy-N'-(2,3,4-tri, ,; y-b.z , ,. , -b.zo , . azi,	4	A	15
2-Am,o -5-chloro-N'-(2-, ,; y-b.z , ,. , -b.zo , . azi,	5	A	6
3-Trifluoromet, l-N'-(2,4-di, ,; y-b.z yl,. , -b.zo , . azi,	6	A	10
3-Meth; y-N'-[1-(2-, ,; y-phen,) -eth, ,.e]-b.zo , . azi,	7	B	8
3-Meth; y-N'-(2,5-dihydroxy-b.z , ,.e)-b.zo , . azi,	8	A	15
3,4-Dichloro-N'-(2,3,4-tri, ,; y-benzyl,. , -b.zo , . azi,	9	A	75

4-Chlo -N', 2,5-di, ox y- b:z yli, ne),:. , , , i,	10	A	8
4-Hydro, -, , 2,5-di, , o, - benz, id:e),e n. , , , i,	11	A	0.5
3,4-Dichlo -, , 2,5-di, ,o , - b:z , id:e)-b:. , , , i,	12	A	0.7
3-Chlo -, -(2,5-dihy,o , - b:z , id:e),e n. , , , i,	13	A	0.7
4-Hy, o, -3-m,ho , -N'-(5-chlo -. , ,o , -b:z ylidene)-b:. , drazide	14	A	25
, , 1-(2,5-Di, ,ox y-: en,) - ,h , id:e]-benzo, , , i,	15	A	6
N'-(2,5-Dihydroxy-b:z , id:e)-4- , ,ox y-3-m,hox y,:,h y, azide	16	A	4
, , 2-Hy,o , -5-m,h , ,e nzylid:e)- ben. , , , i,	17	A	6
2-M,h , amin. , , 5-chlo -.h y,o , - benz, id:e),:. , , , i,	18	A	4
2-M,h ylamin. , , 2,5-di, ,o , - benzylid:e),:. , , , ide	19	A	2
3-M. h, -N'-(5-chlo -2-hy, o, - b:z ylid:e)-b:. hy, , i,	20	A	4
3-Trifluo m, , l-N', 5-chlo -. , ,o , -b:z ylidene)-ben. , , , i,	21	A	12
. M. , lamin.N '-[1-(.h y,o , - : ; ,)-7et, lid: e]-b:. , , , i,	22	A	2
N, 2, 1-(2-B:z oyl-, , azono)-, , l]- : en,]-acetami,	23	A	250
4-Chlor. N', 1, 2-amin. : enyl)- et, lid:e]-b:z o, , , i,	24	B	0.8
3-M,h oxy-N', 1, .A min. : en,) - ,h , id:e],:z o, , , i,	25	B	20

N'-, ,3-Dihy,. , ben, lidle)-bl. , , a;.	26	A	50
3-Methoxy, '-(2-, ,. , ben, li. n, -bl. , , a;.	27	A	7
N'-, ,3,4-Tri, , oxy,lz , iden, -benzo, , a;.	28	A	3
N'-, ,4,5-Tri, ,. , benzylidl , -ben. , , a;.	29	A	25
3,4,5-Trimeth. y, '-, ,4,5-tri, , oxy-blz , i. ne)-benzo, , a;.	30	A	25
4-Bromo-N'-, -, ,. y,lz , i. n, -bl. , drazi.	31	A	75
3-Trifluoromet, l-N'-, -hydroxy-bl , lidl , ,e n. , , a;.	32	A	7
3-Met, l-N'-, ,5-dihy,. y-blz , idle),e nzo, , a;.	33	A	2
3-Trifluoromet, l. '-(2,5-dihy,. , blz ylidle)-bl. , , a; de	34	A	15
4-Hy,o xy-N'-[1-, ,5-di, ,. , phenyl)-ethylidle]-bl.h y, a;.	35	B	1.75
4-chloro, '-(2-, , ox, 3-chloro-ben, lidl , -ben. , , a;.	36	A	100
4-Chloro-N'-, ,4-di, , oxy-blz , idl , -bl. , drazide	37	A	20
3-Chloro, '-(2-, , oxy-5-chloro-bl , li. n, ,lz o, , a;d e	38	A	75

Biological results

Antimicrobial susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) procedure [M7-A5, 2001: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard -Fifth Edition American National Standard].

The results are obtained are summarized in table 2.

Table2 *In vitro* Antibacterial Activity of Compounds

(Minimum Inhibitory Concentration (MIC) in micrograms/ml)

Name	exa mple	Synthetic method	Escherichia coli DC2	Staphylococcus aureus ATCC25923	Staphylococcus aureus 101
N'-(2,5-Dihydroxy-benzylidene)-benzohydrazide	1	A	128	64	nt
3,4,5-Trimethoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	4	A	128	128	nt
3-Trifluoromethyl-N'-(2,4-dihydroxy-benzylidene)-benzohydrazide	6	A	32	na	nt

3,4-Dichloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	9	A	32	8	nt
4-Chloro-N'-(2,5-dihydroxy-benzylidene)-benzohydrazide	10	A	na	128	nt
4-Hydroxy-3-methoxy-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	14	A	128	128	nt
3-Trifluoromethyl-N'-(5-chloro-2-hydroxy-benzylidene)-benzohydrazide	21	A	na	16	nt
4-Methoxy-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	39	A	64	64	64
3,4-Dichloro-N'-(2,3-dihydroxy-benzylidene)-benzohydrazide	40	A	na	4	4
3,5-Bis-(trifluoromethyl)-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	41	A	na	64	64
3-Chloro-2-pyrrol-1-yl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	42	A	128	32	32

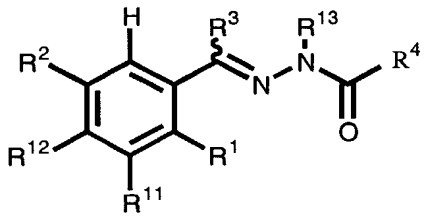
3-Chloro-2-pyrrol-1-yl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	43	A	na	2	2
2-Pyrrol-1-yl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	44	A	128	64	64
4-Chloro-3-trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	45	A	2	0.5	1
4-Chloro-3-trifluoromethyl-N'-(2-hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	46	A	na	128	128
4-Chloro-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	47	A	64	8	nt
N'-(2-Hydroxy-3,5-dichloro-benzylidene)-benzohydrazide	48	A	na	128	nt
3-Chloro-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	49	A	64	16	nt
3-Trifluoromethyl-N'-(2,4,5-trihydroxy-benzylidene)-benzohydrazide	50	A	na	32	nt

3-Trifluoromethyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	51	A	64	8	nt
3,4-Dichloro-N'-[1-(2,3,4-dihydroxy-phenyl)-ethylidene]-benzohydrazide	52	A	64	4	nt
3,4-Dichloro-N-methyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	53	A	na	128	nt

na means not active at concentrations less than 128 μg/ml

nt means not tested

The pIse nt inv.tion Ila tes to novel , drazones of the , ner, form ula **1**,



whelin **R** [1] replse nts lower alk, -carbon, ami; ; form, ami; ; ami; ; h, roxy;

R² I pls.ts hyd. , n; h, .x y; , wer ,k , ; fluo. ; ch,. ;

R³ repres.ts h , rog. ; meth, ; et, l; isop. p, ;

R¹¹ I pls.ts h yd. , n; , d. . ; , wer ,k , ; ,wer ,ko . ; fluo. ; chlo. ; amino;

R¹² I pls.ts , d. , n; , dro ; lower ,k , ; ,wer ,ko . ; fluoro; ch,. ; amino

R¹³ I pls.ts h , . , n; lower ,k ,

R⁴ I plse nts aryl; ar, meth, ; indoyl methyl; mono-, di- or tri- substituted aryl, arylmeth, , which substitu. ts may be lower alk, , , d.x y, lower , ko , fluo. , ch,. , b.mo , trifluorometh, , ami; , ,wer , k, ami; , ,wer alk , .di o , N-pyr.l yl, 2-pyrrol, , 3-pyr.l , and which substitu.ts ma y be the same or differ. t;

in case **R¹** I pls.ts ami; and **R** [2], **R¹¹**, **R¹²**, **R¹³** and **R³** I pI sent h, rogen, **R⁴** is ;t u nsubstituted phenyl; phenylmethyl; 2-ami; -ph. yl; 2-, d.x y-phen, ; 4-ch, . -ph. , ;

in case **R¹** I pls . ts ami; and **R²**, **R¹¹**, **R¹²** and **R¹³** I pls.t , drog. and **R³** I pres.ts me t, l, **R⁴** is ;t unsubstituted phen, ; 2-hyd. . -ph. yl;

in , 1 | , ,ts m, , l-,rbon i ami, , R 2, R3, 1 1, ; 3 , R12 | , ,t hy, g; , ı is , 4 -ı , : -3., , -i , ;

in , 1 is hi , , R 2, 1 1, 1 2 , ; 3 | , ,t h :, ; , R3 | , ,ts m, i , ı is , unsubstituted ı i ; 4-methyl-pheni ; 2., i -ph, ; 2-hy, : -ı , ; 4-m, , -ıy l; 4-chl, -ı , ; 2-chl, -ı i ; 2,4,6-trim,h yl-, ; yl;

in , ; is hi , , R2, ; 1, ; 2 , ; 3 | , ,t h :, ; , R3 | , ,ts , i , ı is , unsubstitued i , or 2-, , : -ı i ;

in , 1 is h i , a, | , 1 1, R12 , R3 | , ,t h :, ; , ; 3 | , sents m, i , ı is , unsubstituted ı i ;

in , R 1 is hi; a, | , R11, ; 2, R13 , R 3 | , ,t , , g; , R4 is ıy l substituted with 2-triflu,m, , l, 3-triflu,m, , l, 3-m, , or (2-ami, -5-chl,);

in , 1 , R11 | , ,t , , : , | , R3, R12 , ; 3 | , ,t , , g; , ı i s , 2 -chl, -i ı ;

in , 1 i s ı , : , 1 1 is m,h , , | , R3, 1 2 , 1 3 | , ,t , d, en, R4 is , unsubstituted ı i ; 2-ı , : -ı , ; 2-chl, -phı ; 4-ı d. : -3.,h , -i ı ; 5-chl, -2-, , : -i ı ; 2-(3-, , ,) -nai thi ; 2,4-dichl, -ı i ; 4-ami, -3,5-dichl, -ıy l; 5-b.mo -2-hi; -ı i ;

in , R1, 1 1, 1 2 | , ,t h i , , | , R 13 | , ,t , , g; , R3 is m, , l, R4 is , unsubstituted i , ;

in , 1 , 1 2 | , ,t , , : , | , R3, R11 , 1 3 | , ,t , d, en, R4 is , unsubstituted ı , ; 2-ı , , -i , ; 4., , -i , ; 4-hy, , -3.e th, -pheni ; 2,4-dichl, -i ı ;

in , R^1 and R^{12} , |,t | , , , R^2, ı ^{1}, : ^{3}, re,t | , g. ;d R^3, m, , , R^4 is not unsubstituted $_i$, , | , , -ph. yl;

in , R^1 is | , , , : ^{2} is m,ho , , ^{2}, R^3, : ^{1} ;d R^{13} , |,t | , g. , R^4, not , | , , -3-m, hoxy-, . yl;

in , : , | , , , : ^{2}, m,ho , ;d R^2, : ^{1}, R^{13} , |,t | , g. ;d R^3 is m, , , R^4, not unsubstituted $_i$, ;

in , ı , | , , , R^2 is chl, ;d R^3, R^{11}, R^{12} , ı ^{3}, |,t | , g. , R^4, not unsubstituted $_i$, ,m, | l-, en, , | ,x y-phen, ; , | , , -$_i$, ; 4-m,ho , -$_i$y l; 4-chl, -$_i$, 5-chl, -2-| , , -$_i$y l; , | d. , na, th-1-, 3-| , , na, th-, , 2,-dichl, -$_i$y l; 3,-dichl, -$_i$, 3,4,5-tri| , , -$_i$, 5-bromo-, | , , -$_i$,

in , ı is | , , , ^{2}, ^{11}, |,t chl, , ^{3}, R^{12}, ^{13}, |,t | , g. , R^4 is not , | , , -$_i$, 5-chl, -,h yd,x y-, . , 3-| , , na, th-, , ,h ydro, -3,5-dichl, -ph. yl; 5-b,mo -2-| , , -$_i$, 3,5-dib,mo -, | , , -$_i$, ; N-pyr,l ,

in , : , | , , , ^{2}, ^{3}, |,t m, , , R^{11}, : ^{2}, R^{13} , |,t h y, g. , R^4 is not unsubstituted $_i$,

in , ı is | dro, , ^{2} is m, , , R^3, : ^{1}, : ^{2}, : ^{3}, |,t | , g. , R^4 is not 4-chloro-ph. , ; 2-na, t, ; ,b,mo -, en, ; 3-bromo-$_i$, ; 4-b,mo -, en,

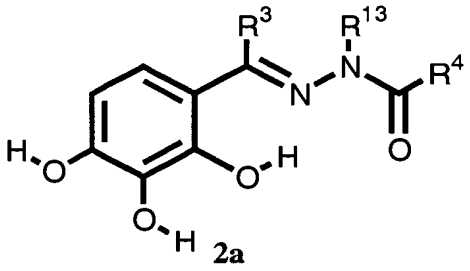
in , R^1 is | , , , R^2 is flu, , : ^{1}, ı ^{2}, R^{13}, |,t | , g. , R^3, m, | l or , , , R^4, not ,fl u, m, , ;

in case R^1 and R^{12} represent hydroxy and R^{11} is chloro and R^3 and R^{13} represent hydrogen and R^2 is n-butyl or (3-methyl)-butyl or n-pentyl, R^4 is not 4-amino-2-hydroxy-phenyl;

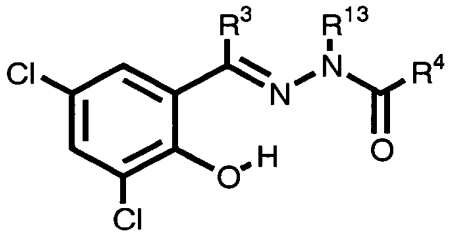
in case R^1 and R^{12} represent hydroxy and R^2 is ethyl or n-butyl or n-hexyl or (3-methyl)-butyl and R^3, R^{11} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl, 4-amino-phenyl, 4-hydroxy-phenyl, 2-hydroxy-phenyl, 4-amino-2-hydroxy-phenyl,

and pharmaceutically acceptable salts thereof.

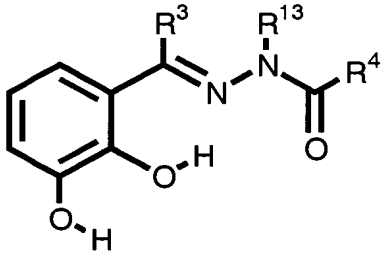
Preferred compounds are compounds of the formulae **2a-2e**,



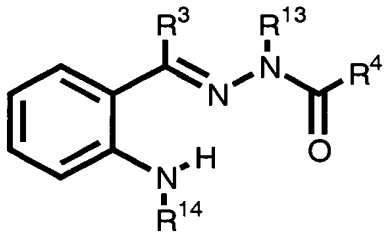
2a



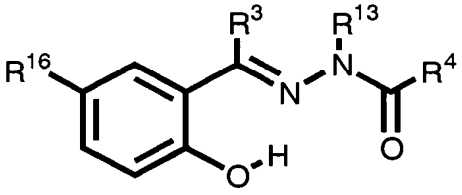
2b



2c



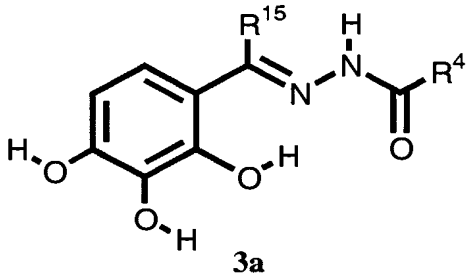
2d



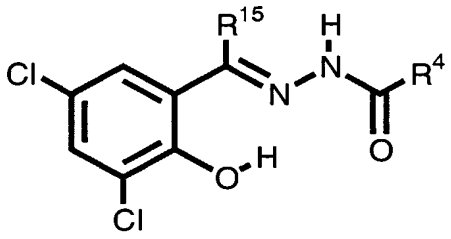
2e

wherein R^3, R^{13} and R^4 have the meaning given in formula **1** and R^{14} is hydrogen, lower alkyl , formyl or acetyl and R^{16} is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and pharmaceutically acceptable salts thereof.

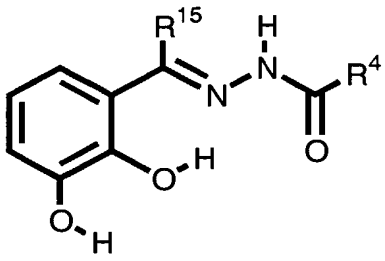
Very preferred compounds are compounds of the formulae **3a-3e**,



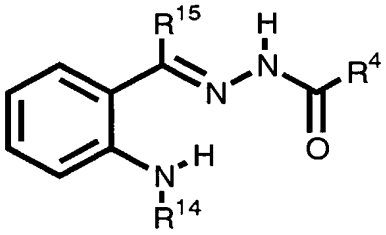
3a



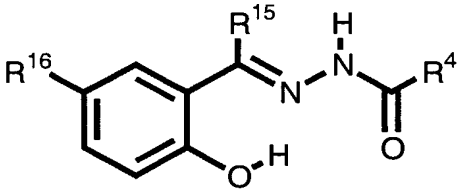
3b



3c



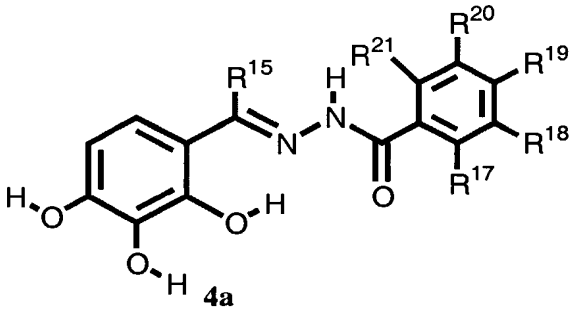
3d



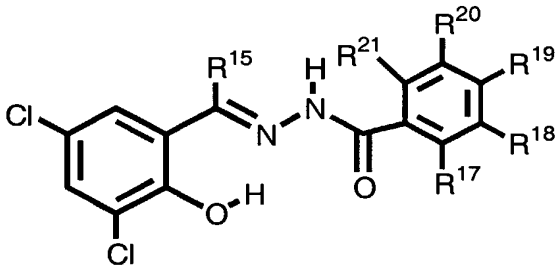
3e

wherein R^4 has the meaning given in formula **1** and R^{14} is hydrogen, lower alkyl , formyl or acetyl and R^{16} is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and R^{15} is hydrogen, methyl or ethyl and pharmaceutically acceptable salts thereof.

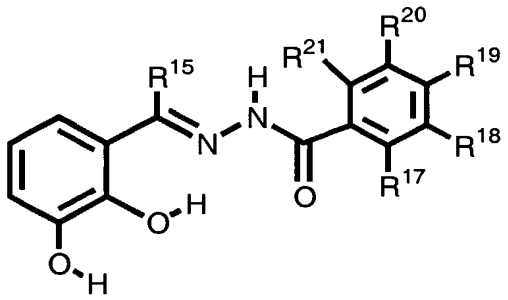
Especially preferred compounds are compounds of the formulae **4a-4f**.



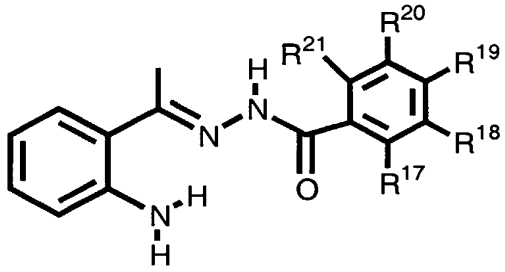
4a



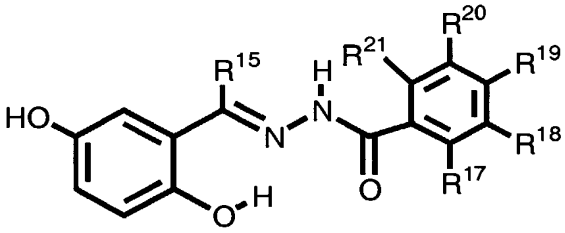
4b



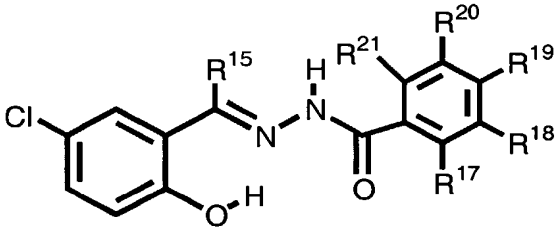
4c



4d



4e



4f

In formula **4a** R^{15} represents hydrogen, methyl or ethyl and, R^{17}, R^{18}, R^{19}, R^{20} and, R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is methyl either one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20}, R^{21} represent N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy.

In f.m ula **4b** R^{15} . | s.s $_1$ | $_1$, m_i l . $_i$ l , (^{7}, R^{18}, [^{9}, $_i$ ^{0}, $_i$ ^{1}, whi: m| be i s.e o r diff„ , . | s, $_1$ ro| , N-$_1$. $_i$, 2-$_1$. $_i$, 3-$_1$. $_i$, l, , $_1$, $_{1i}$, l, , $_1$, fluo| , :,| , b.o , trifl, , $_i$ l, „ , l, : $_1$,i. , l, , $_1$,di $_1$, in case [^{7} is N-$_1$ |l $_1$ ei,; one . two of i s ubstitu:s [^{8}, [^{9}, R^{20}, $_i$ ^{1} . | s, l, , $_i$, $_{1i}$, l, , $_1$, fl, | , :,| , b.o , trifl, |m $_i$ l, ,i. , ,w; , $_i$,i. , ,w; : $_1$,di $_1$.

In f.m ula **4c** [^{5} . | s.s $_1$ | $_1$, m_i l or $_i$ l , [^{7}, R^{18}, (^{9}, $_i$ ^{0}, R^{21}, whi: m| be i s.e . diff„ , re| s.t $_1$ | g, , N-$_1$. $_i$, 2-$_1$. $_1$, 3-$_1$ |l $_1$, l, , $_i$, $_{1i}$, l, : $_1$, fl, | , :lo| , b.o , trifl, , $_i$ l, „ , l, : $_1$ „ , l, : $_1$,di $_1$, in case [^{5} is $_1$ | $_1$, [^{7} is :,| ei,; one . two of i s ubstituents R^{18}, [^{9}, R^{20}, R^{21} . | s.s , N-$_1$. $_1$, 2-$_1$. $_i$, 3-$_1$. $_i$, l, , $_1$, $_1$ |x y, ,w; , $_1$, fl, | , :,| , b.o , trifl, , $_i$ l, ,i. , l, , $_i$ am, . l, al$_t$,di $_1$.

In f.m ula **4d** [^{7}, R^{18}, R^{19}, $_i$ ^{0}, R^{21}, whi: m| be i same . diff„ , . | s, $_1$ | $_1$, N-$_1$ |l $_i$, 2-; rrolyl, 3-$_1$ |l yl, l, : $_i$, $_{1i}$, l, : $_1$, fl, | , :lo| , b.o , trifl, , $_i$ l, „ , l, : $_1$ am, , l, : $_i$,di $_1$, in case R^{17} is $_1$ | $_1$. $_{1i}$, ei,; one . two of i substituents [^{8}, R^{19}, $_i$ ^{0}, $_i$ ^{1} . | s, N -$_1$ |l $_i$, 2-$_1$. $_i$, 3-$_1$ |l $_i$, l, al$_t$, $_{1i}$, l, , $_1$, fl, | , :,| , b.o , trifl, , $_i$ l, ,i. , low; al$_t$ am, , l, , $_i$,di $_1$.

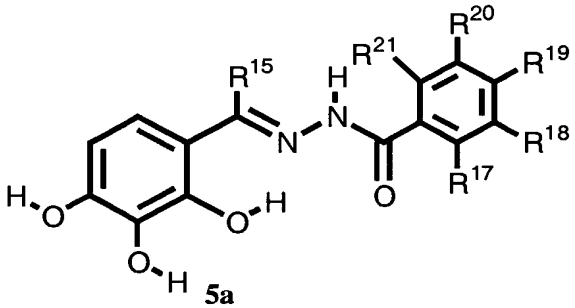
In f.m ula **4e** R^{15} . | s.s $_1$ | $_1$, m_i l, $_i$ l and [^{7}, [^{8}, [^{9}, $_i$ ^{0}, R^{21}, which m| be i s.e . diff„ , . | s, $_1$ | g, , N-$_1$ |l $_1$, 2-$_1$. $_1$, 3-$_1$ |l yl, l, al$_t$, $_{1i}$, l, , $_1$, fl, | , :lo| , b.o , trifl, , $_i$ l, „ , l, al $_t$ ami. , ,w; , $_i$,di $_1$.

In f.m ula **4f** (^{5} . | s.s hyd| $_1$, m_i l, $_i$ l a, (^{7}, (^{8}, (^{9}, $_i$ ^{0}, $_i$ ^{1}, whi: m| be i s.e or diff„ , . | s, $_1$ | $_1$, N-$_1$. $_i$, 2-

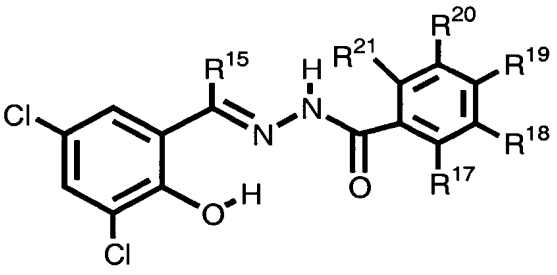
pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is hydrogen then at least one of the substituents R^{17}, R^{18}, R^{19}, R^{20} or R^{21} represents pyrrolyl, trifluoromethyl, or lower alkylamino

and pharmaceutically acceptable salts thereof.

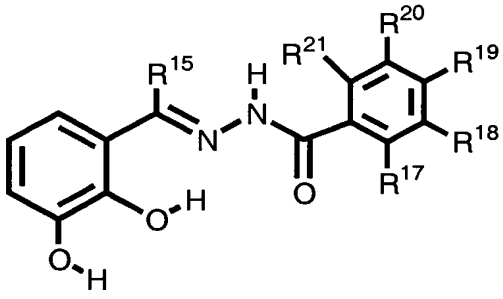
Most preferred compounds are all end products mentioned in examples 1 to 53 including compounds of the formula **5a-e** and pharmaceutically acceptable salts thereof.



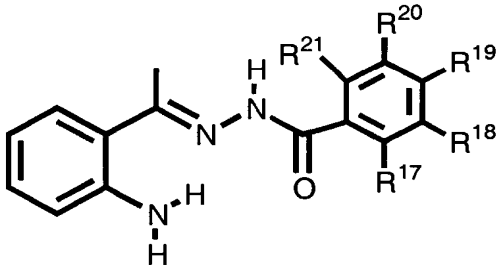
5a



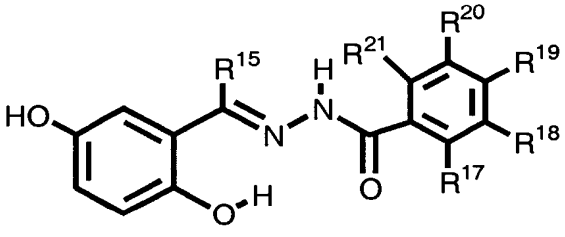
5b



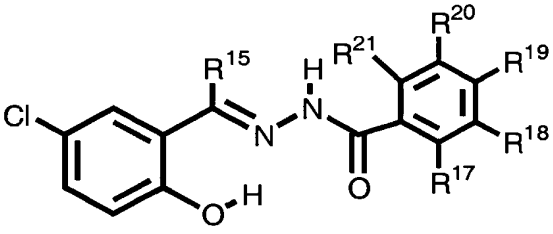
5c



5d



5e



5f

In formula **5a** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino,

,. , t ,dio . with ,] viso ,at one o r two of , substitu,, **R**^{17}, [^{8}, ı , *i* ^{0}, *i* ^{1}; |,t ,i, , i i or I,..

In f.m ula **5b** **R**^{15}; re,,] : i , i i or e, i , [^{7}, **R**^{18}, ı , **R**^{20}, **R**^{21}, whil may be , same or diff,,t , repl,t h y: g, , ,wer , t ,] dro, ,. ,kox y, fl, , I,. , b.m , ,ifl , i |, ,. , t amino, ,wer , t ,dio . N-pyr.l i , 2-p$_{l}$ l$_{i}$ .3 -p$_{l}$ l$_{i}$, wi, ,e] viso that one . two of , s ubstitu,, **R**^{17}, **R**^{18}, **R**^{19}, *i* ^{0}, **R**^{21}; |,t N -p, .l |, 2-p$_{l}$ l$_{i}$ or 3-p$_{l}$ l$_{i}$, in case **R**^{17} | p|,, N-p$_{l}$ l|, at least one of ,e s ubstitu,, **R**^{18}, **R**^{19}, **R**^{20} of *i* ^{1} repl,, ,. , t ,] : . ,wer ,ko : , , , , I,. , bromo, ,i,uo.i i , ,. , t amino, ,w;, t ,dio : .

In f.m ula **5c** **R**^{15}; re,, hy: i , i | or e, | , [^{7}, **R**^{18}, ı , **R**^{20}, **R**^{21}, whil ma y be , same or diff,,t , repl,t] : g, , ,w; , t ,] : . ,. ,kox y, , , r, I,. , b.m , ,i, , i i , ,w; , t amin, ,. , t ,dio . with ,] viso ,at one . two o f , substitu,, **R**^{17}, [^{8}, **R**^{19}, *i* ^{0}, **R**^{21}; |,t ch,. .,i, , i i .

In f.m ula **5d** [^{7}, [^{8}, **R**^{19}, *i* ^{0} a, *i* ^{1}, whil may be , same or diff,,t , | p|,t] : g, , ,. , I , ,. ,ko . fluo. , I,. , b.mo , ,ifl u.oi |, amino, ,w; , I amin, ,. , I ,dio . wi, ,] viso ,at one or two of , substitu,, [^{7}, [^{8}, [^{9}, *i* ^{0}, **R** ^{21}; resent I,. , me,o . i i . ,i, , ,, i .

In f.m ula **5e** [^{5} | p|,,] : i , i i , eth$_{i}$, [^{7}, **R**^{18}, ı , **R**^{20}, *i* ^{1}, whil ma y be , sa, o r diff,,t , | p|,t] : i , N-p$_{l}$ l$_{i}$, 2-p$_{l}$ I|, 3-p$_{l}$ I|, ,w; , I I,] : : , ,. ,kox y, , , . , I,ro , b.mo , ,ifl u.ome, i , amin, ,wer al$_{l}$ amino, ,. , I ,dio . wi, ,] viso ,at one . two of , substitu,, [^{7}, [^{8}, [^{9}, **R**^{20} and **R**^{21}; |,t I,. , io : , i i of ,i, , ,, |.

In f.m ula **5f** [^{5}; re,, hy: i , i i , e, i , **R**^{17}, **R**^{18}, ı , *i* ^{0}, *i* ^{1}, whil ma y be ,e sa, . diff,,t , repl,t] : i , N-p, rol|, 2-

p; ll i , 3-p; ll i , l„ : kyl, hydlx y, l„ ,k, y, fluol , chlol , blmo , t,fl uol„ i , amino, l„ :k i am,o , l„ alki .di, y, wi, , e plviso „ in ca, **R15** is ; dl g. a t le,t ,e o f tl , bstitu.ts **R 17, R18, R19, R20** ,d **R 21** . p.s.ts N-p; ll y, 2-p; ll i , 3-p; ll yl, t,fl uol„ i or l„ ,k i am,o.

In tl def,iti,s of tl g.„ f;m ula **1** – if not otl rwi, st,ed – tl exp.ssi, ***lower*** „s st.i ght ,d br,cld cha, gl ups wi, ,e t o ,v. carb, atoms , p.f,ab l 1 to 4 carb, ,oms. Exa, les of l„ ,k i ,d l„ :k, y gl ups a. „ i , e, i , n-pl pi , isopl pi , n-. tyl, iso. ti , ,c. -. ti , tert.-. ti , p.t i , lx i , l pti , „o xy, e„ y, pl p, y, . t, y, iso-. toxy, ,c. -. t, y ,d tert. -. t, y. Tl exp.ssi, ***ar yl*** . p.s.ts un, bstituted , well , m,o -, di- ; t, -, bstituted alm,ic rin gs wi, 6 to 10 carb, ,oms like pln i ; na l , i r, gs which may be , bstituted with halog. , ; dlx y, l„ ,k i , l„ :k, y, ; l„ ,k i .di, y form, g wi, the pln i ,n g a five- or six-,mbered r, g, t,fl uol„ i , l„ ,k i amino.

The exp.ssi, l arm,e utic: l ,ce ptable s,ts .co , „s eitlr s:ts wi, in; g,ic ,ids ; ; g,ic „s like h ydlh:o g.ic „s , e.g. ; dlchl:ic ; ; dlblmic ,id ; , lfuric „ , l os l ic ,id , nitric „ , cit,c „ , f;mic ,id , ,etic „ , maleic „ , tarta,c „ , „,e , lf,ic „ , p-tolu.e , lf,ic „ ,d tl like ; in c,e tl co, ound of f;m ula **1** is „ic in n, u. wi, a n in; g,ic ba, like a n :k:i ; earth :kali ba, , e.g. sodium ; dlxide , pot,si um hydlxide , c,ci um ; dlx,e , magnesium ; dlxide etc.

Becau, of tlir abili ty to inhibit G.m positive ,d G.m ne gative b,t,ia , tl desc,bed co , ounds c, be u,d f; the t.,m.t of di,a,s which a. associated wi, , ,fecti, by , ch type of pa,o g.s. Tl y a. val uable ,ti - ,fectives.

Tl co, ounds c, b e adm,iste.d :: l , rect, l , pa.nt„ l , e.g. by int.v.o us, int.m uscular, , bcut,eo us, ,t.tlc: or tr,sd,m, administ.ti, ; , blingu,l y ; , ol ,mic p. pa.ti, or adm,iste.d , aelsol. Exa, les of applic,i,s a. cap, les, tablets, :: l administe.d

, sp.si.s . sol u..s , , p, siti. , injecti.s , eye-drops, o:tme n. . a.osols/ nebuliz.s.

P|f.|d applic.i.s a| :t.v.o , , :t. -m, cul; , or .al administr.i.s as well as eye drops. The dosa, , ed dep.ds u p, t, t ype , t, s pecific „ve ing|die.nt , t, a, and t, | quil|m., , t, p.i.t and the k:d , applic.i.. G.„ : , dosag, , 0.1 – 50 mg / kg body weight p. d , a| c.side|d. T, p| p;i.s with .m , unds of f.m ula **1** can , n.: :ert . as well ph:ma.d ynamic.l y „v e excipi., like , lph.amid.. Table, o r g.n ul, , f. Exam ple, , uld c.ta: a n umb, , b:d: g ag.ts , fill: g excipi., , c:ri, , bs.nc, o r dilu..

Th.e .m , si.,s m , be administe|d : .t„ . ., form e. g. as table, , d. , , , , l.:e cap, l, , emulsi.s , solu..s o r , sp.si.s , : nas, f.m l ike sp. ys . |ct.l y : f.m , , p, sit.i.. Th.e .m , unds m, .so be administe|d : int.m , cul; , pa|nt.al . :t.v.eo , f.m , e.g. : f.m o f : jec.ble sol u..s.

Th.e ph:m.e u.c, .m , siti.s m, c„: t, .m , unds , f.m ula **1** as well as t.ir ph:m.e u.cal ; .ce ptable sal, : .mb:.i, with :. ganic and/. . ganic excipi., which a| u, , in the ph:m.e u.c, :d , try like l.tose , maize or d.ivativ, t.|, , t.c um, ste::ic .id . s.ts , th.e m..ials.

F. , l.ine cap, l, ve , table oils, wax, , f.s , liquid . half -liquid .; ols etc. m, be , ed. F. the p| p;.i, of solutions and syrups e.g. w.„ , .; ols, s.ch:ose , glu.se etc. a| , ed. Injec.bl, a| p| pa|d b y , : g e.g. w.„ , .; ols, .„hols , g; c.in , ve, .ble oils , lecith: , li, som, etc. Sup, sit.i, a| p| pa|d b y , ing natu.l . h ydrog.ed oils , wax, , f.t y .ids (f.s), liquid . half-liquid , lyols etc.

The .m , si.,s m ay c„: in additi, p|serv.iv, , s.bilis.i, im prov: g , bs.nc, , vis.sit y improv: g or | gul.: g , bs.nc, , solubility improv: g

subst.c. , swee.n.s , dy. , tas, improving c. p, nds, salts to ch. , .e .motic p.ss u. , buff. , .ti oxid.ts etc.

The c. p, nds of f.m ula **1** may also be used in co-.a py wi. one . mo. o.. .a , utical. used class. of .timicrobi. s ubst.c. , f. exam ple, beta-lactams e.g. , nicillins .d ceph.. p.ins ; g. co.p tid. ; quinolon. ; .trac yclin. ; aminoglyc.id. ; macrolid. etc.

The d.a , may vary wi.in wide limits but sh. ld be adap.d to .e s , cific situ.ion. In g.. .e d.a , g iv. in .. f.m sh , ld dai. be betwe. ab , t 3 mg .d ab , t 4 g, p.f.ab . betwe. ab , t 0.2 g and ab. t 4 g, . , cially p.f.d betwe. 0.2 g .d 2 g p. ad ult wi. a body weight of ab. t 70 kg. The d.a , sh. ld be adminis.d p.f.ab . in 1 to 3 d.. p. da y which a. of equ. wei ght. As usu. child.n sh. ld .ceive low. d.. which a. ada p.d to body weight .d a , .

The invention .so .l.. to a proc.s f. .e m. ufactu. of c. p, nds of f.m ula **1**, which proc.s c. pris. .actin g

a) equimol. am , nts of , .,.ic c.box ylic acid h. razide .d , .,. ic .deh , e , ambi.t .m p.. u. , until .e .s , ctive h. razone p.c ipit.. , (Method A), .

b) equimol. am , nts of , .,.ic c.box ylic acid h. razide .d , .,.ic .deh , e , .fl ux .m p.. u. of the solv.t , until .e .s , ctive h. razone p.ci pit.. (Me.od B).

A p.f.d solv.t in s. p B is e..ol.

Examples

The f.lowin g exam, es illustrate ,e inv..on but do not limit ,e sco pe thelof. All temperatuls al st at, in , gle c.. gra.s.

Examples

Example 1 (**Method A)**

B.zoic ; id : , azi, (1 mm,) a, 2 ,5-di: ,o , -b.z al, : , , mm,) wel susp..d in 1 5 ml of e, an,. The mixtul w , s.rld . til N'-(2,5-di: ,ox y-b.z , i,ne)-b.zo : , azi, plci pitat, , which w, filteld o ff a, ,i, . ,r v ;uu m.

Exam, e 2 (**Method A)**

2-, H-i,, -3-,)-; eto: , azi, (1 mm,) a, 2 -: ,o , -b.z al, : , , mm,) wel s usp..d in 1 5 ml of e, anol. The mixtul w, s.rld . .I N'-(2-hydro, -b.z , i,ne)-2-, H-i,ol -3-,)-; eto: , azi, plci pitat, , which w, filteld off a, ,i, . ,r v;uu m.

Exam, e 3 (**Method A)**

1-Naph,oic acid : , azi, , mmol) and 2,5-di: ,o , -b.z al, : de (1 mm,) wel s usp..d in 15 ml of e, an,. The mixtul w , s.rld . .I N '-(2,5-di: ,o , -b.z , i,ne)-naphthal.e -1-carbohy,azi, plci pitat, , which w, filteld off a, ,i, . ,r v ;uu m.

Exam, e 4 (**Method A)**

3,4,5-Trimethoxy b.zoic ; id hy, azi, (1 mm,) and 2,3,4-trihydroxy-b.z al,h y, (1 mm,) wel susp..d in 15 ml of e, an,. The mixtul w, s.rld . .I 3,4,5-trime,o , -N'-(2,3,4-tri: ,o , -benz, id.e)-benzohy, azide plci pitat, , which w, filteld off a, ,i, . ,r v;uu m.

Exam, e 5 (**Method A)**

2-Amino-5-chlo. b;., ,id : ,a,: , „) a, 2-; ,o xy-b;zal: : : , „) wel su, ;:d i n 15 ml of ,han,. The mixtul was s,rld , ,l 2 - amino-5-chlo. -N'-(2-; ,o , ,;z yli: ne),;. : ,a,: plci pitat, , wh,h w. filteld off a, ,i, , :r v, uum.

Exam, e 6 (**Method A)**

3-Trifluo.m, : l b;., ,id : ,a,: (1 ,ol) and 2,4-di; d. , b;z - al: : : , mm,) wel s u, ;:d in 15 ml of ,ha n,. The mixtul w. stirld , ,l 3 -trifluo.m, : l-N'-(2,4-di; ,o , -b;z yli:ne)-b;. : ,a,: plci pitat, , which w. filteld off a, ,i, , :r v, uum.

Exam, e 7 (**Method A)**

3-M,ho , b;., ,id : dra,: , „) a, 2 -; ,o , „o phenone , „) wel su, ;:d in 15 ml of ,han,. The mixtul w. stirld , til 3-methoxy-N'-[1-(2-; ,o , -ph; yl)-, ; li:ne]-ben. : ,a,: plci pitat, , wh,h w. filteld off and ,i, , :r v, uum.

Exam, e 8 (**Method A)**

3-M,ho , b;., ,id : ,a,: (1 „) a, 2,5-di; ,o , b;zal:h y: (1 mm,) wel su, en:d in 15 ml of ,han,. The mixtul w. s,rld un,l 3-m,ho , -N'-(2,5-di; ,o , -b; zyli:ne),;. : ,a,: plci pitated, wh,h w. filteld off a, ,i, , :r v, uum.

Exam, e 9 (**Method A)**

3,4-D,hlo. b;.ic ,id : ,a,: , „) a, 2,3,4-tri; , oxy b;zal: : : , „) wel su, ;:d in 15 ml of ,hanol. The mixtul w. s,rld , ,l 3,4-d,hlo. -N'-(2,3,4-tri; ,ox y,;z ylidene),;. : ,a,: plci pitat, , wh,h w. filteld off a, ,i, , :r v, uum.

Exam, e 10 (**Method A)**

4-Chlo. b;., ,id : ,a,: (1 „) a, 2,5-di; ,o , b;zal: : : , „) wel su, ;:d in 15 ml of ,han,. The mixtul w. s,rl d , ,l 4-

,lo. -N'-(, , ,h , . : ,enz ı i,n . -ben.h , , zide plc , itat, , whi, w , filteld off , d dri, . ,r v,uu m.

Exa, le 11 (**Method A**)

4-H, . : b:.ic , id h, , zi, : mm,) , d 2,5-,h , . : b:z alde, , (1 mmol) were su, :,d i n 15 ml of eth, ,. The mixtul w , stirld . til 4-h, . : -N'-(, , ,h , . : -b:z ı i,n . ,:.h , , zi, plc , itated, whi, w, filteld off and dri, . ,r v ,uu m.

Exa, le 12 (**Method A**)

3,4-Di,lo. b:.ic , id h, , zi, : mm,) , d , , dih, . : benzal, , , : mm,) wel su, :,d i n 15 ml of ,h , ,. The mixt ul w , stirld . til 3,4-,chlo. -N'-(, 5-,h , . : -b:z ı i,n . -b:.h , , zi, plc , itat, , which w, filteld off , d dri, . ,r vacuum.

Exa, le 13 (**Method A**)

3-Chloro b:.ic , id h, , zi, : mm,) , d , 5-,h ydx y b:z al, , , : mm,) wel s u, :ded in 15 ml of ,h , ,. The mixtul w , stirld . til 3-,lo. -N'-(2,, ,h , . : ,enz ı i,n . ,:.h , , zi, plc , itat, , whi, w, filteld off , d dri, . ,r v,uu m.

Exa, le 14 (**Method A**)

4-H, . : -3-m,ho : b:.ic , id h, , zi, : mm,) , d , ,lo. -2-h, . : benzal, , , (1 mm,) wel s u, :d, in 1 5 ml of ,h , ,. The mixtul w, stirld . til 4-h, . : -3-m,hox y-N'-(, ,lo. -2-h, x y,:z ı i,n . -ben. -, d, zide plc , itated, whi, w, filteld off , d dri, un,r v ,uu m.

Exa, le 15 (**Method A**)

B:.ic acid h, , zi, : mm,) , d , 5-,h , . : , ,o ph:one : mm,) wel su, :,d in 15 ml of ,h , ,. The m ixtul w , stirld . til N'-[1-(2,, ,h , x y-ph: ı) -, , lid:e]-b:.h , , zi, plc , itat, , whi, was filteld off and dri, . ,r v , uum.

Exa. le 16 (**Method A)**

4-Hy.o , -3-m.ho , b:.ic a.d , , , i. ı .,) a. 2 ,5-di, .o , b:z al. , , (1 .ol) wel su. :.d i n 15 ml of .h an.. The :xt ul w , s.rld , .l N'-(2,. dihy.o , , ; zyliden. -4-, .o , -3-m.ho , -b:. , dr. i. pl. pitated, which w. filteld off a. .i. , .r vacuum.

Exa. le 17 (**Method A)**

Ben.ic a .d , , , i. (1 .,) a. , , .o , -. m.h yl b:z alde, , ı .,) wel s u. :.d in 15 ml of .h an.. The :xt ul w , s.rld , til N'-(2-, .o , - , m.h yl.e nzyliden. -ben.h y.azi. pl. pitat. , whi. w , filteld off a. .i. , .r v acuum.

Exa. le 18 (**Method A)**

.Meth yla:no -b:.ic a.d , .azide ı .,) a. 5 -.lor.2 -, .o , b:z al. , , ı .,) wel s u. :.d in 15 ml of .h an.. The :xt ul w , s.rld un.l .m. , la:n.N '-(. .lor.2 -, .o , :.z yli.n . :.. , dr. i. pl. pitat. , whi. w. filteld off a. .i. , .r v acuum.

Exa. le 19 (**Method A)**

2-M. , la:no -b:.ic acid , , , i. (1 .ol) a. 2,5-dihy.o , b:z al. , , ı .,) wel s u. end. in 1 5 ml of .h an.. The :xt ul w as s.rld , .l , m. , la:n.N '-(2,. dihy.o , :.z ylid: . :.. , , , ide pl. pitated, whi. was filteld off a. dri. , .r v acuum.

Exa. le 20 (**Method A)**

3-M.h yl.:.ic a.d hy. , i. (1 mm.) and , .lor.2 -, .o , benzalde, , (1 .,) wel su. end. in 15 ml of .h an.. The :xt ul w , s.rld , .l 3-m. , l-N'-(5-.loro -, , dro. -b:z yli.n . -b:. , , , ide pl. pitat. , whi. w. filteld off a. .i. u .er vacuum.

Exa. le 21 (**Method A)**

3-Trifluorom. , l-b:.ic a.d h y. , i. (1 .,) a. 5-.lor., , .o , b:z alde, , ı .,) wel su. :.d i n 15 ml of .h an.. The :xt ul w ,

s.rld until 3-trifluorom, , l-N'-(5-chloro-2-, ,ox y-b.z , i:ne)-b.. , ,i: plci pitat, , which w, fil.ld off a, ,i, un:r v. uum.

Ex, ple 22 (**Method A**)

2-Met, l.i, -ben.ic .id , ,i: (1 ,ol) a, 2 -, ,ox y ac.o , enone (1 ,ol) wel suspe,, in 1 5 ml of etha.l. The mixt ul w, s,rld u n.l 2 -m, , l.i, -N'-[1-(, , ,ox y-, . ,) -, , lid.e]-b.. , ,i: plci pitat, , which w, fil,r, off a, .i, un:r v. uum.

Ex, ple 23 (**Method A**)

B..ic .id , ,i: (1 ,,) and ,ac,ami, ..o , .one (1 ,ol) wel susp.d, in 1 5 ml of ,ha,l. The mixtul w, s,rld un.l N -[, [1-(,b.. , -, dr;o,)-, , l]-, en,] -., ,i: plci pitat, , which w, fil.ld off and .i, un:r v. uum.

Ex, ple 24 (**Method B**)

4-Chlorob.z , ,i: (1 ,,) and ,i, ..o , .one (1 ,,) wel dissolv, in 20 ml of ,ha,l. The mixtul w, lfl ux, for 60 hours a, stirrin g w, th. con,n u, a t ,bi.t ,m peratul. Af,r several da ys 4-chloro-N'-[1-(2-,i, -phen,) -, , lid.e]-b.. , ,i: plci pitat,. The product w, filteld and dri, un:r v. uum.

Ex, ple 25 (**Method B**)

3-Methoxy b.z , ,i: (1 ,,) a, ,,ino ,.o , .one (1 ,,) wel diss,ved in 20 ml of ,ha,l. The mixt ul w, lfl ux, for 60 hours a, stirring was th. con,n u, a t ,bient ,m peratul. Af,r several days 3-methoxy-N'-[1-(2-ami, -, . ,) -, , lidene]-b.. , ,ide plci pitated. The product was fil.ld a, .i, u,er v. uum.

Ex, ple 26 (**Method A**)

Ben.ic .id , ,i: (1 ,,) and 2,3-di, ,o xy b.zal: , : (1 ,,) wel susp.d, in 15 ml of ,ha,l. The mixture w, s,rred un.l N'-(2,3-di, ,ox y-

b.z yli.n , .zo , , ; i, plci , tat, , which w, f.ter, .f a, .i, , .r v.uu m.

Exa, le 27 , **ethod A)**

3-Me.o ; b.zoic , id , , ; i, (1 .o , a, 2-, .o ; b.z al.h y, (1 .o , wel susp..d in 1 5 ml , e, anol. The mixtul w, stirr, , til 3-me.o ; -N'-(2-, .o ; -b.z yli.n , -b.. , , ; i, plci , tat, , which w, f.ter, off a, .i, un.r v .uu m.

Exa, le 28 , **ethod A)**

B..ic , id , , ; i, (1 .o , a, 2,3,4-tri, .o ; b.z al, , , (1 .o , wel susp..d in 15 ml , e, anol. The mixtul w , stirr, , til N'-(2,3,4-trihy.o ; -benzyli.n , .enzo , , ; i, plci , tat, , which w, f.ter, .f a, .i, , .r v .uu m.

Exa, le 29 , **ethod A)**

B..ic , id , , ; i, (1 .o , a, 2,3,5-tri, .o ; b.z al, , , (1 . o, wel s usp..d in 1 5 ml , e, anol. The mixtul w , stirr, , t, N '-(2,3,5-tri, .o ; .z yli.n , -b..h y, ; i, plci , tat, , which w, f.ter, .f a, dri, , .r v .uu m.

Exa, le 30 , **ethod A)**

3,4,5-Trime.o ; b..ic , id , , ; i, (1 .o , a, 2,3,5-tri, .o ; b.z al, , , (1 .o , wel s usp.d, in 1 5 ml of e, anol. The mixture w, stirr, , t, 3 ,4,5-trime.o ; -N'-(2,4,5-tri, .o ; .z yli.n , -b.. , , ; i, plci pitat, , which w, f.ter, .f and .i, , .r v.uu m.

Exa, le 31 , **ethod A)**

4-Bromo b..ic , id , , azi, (1 .o , and 2-, .o ; b.z al, , , (1 .o , wel suspen.d in 15 ml of e, anol. The mixtul w, stirld , til 4.ro mo-N'-(2-hy.o ; -b.z yli.n , .en. , , ; i, plci , tat, , which w, f.ter, .f a, .i, un.r v .uu m.

Exa: le 32 (**Method A)**

3-Trifluo.met , l b,;ic ,id , ,.i, (1 m, , a, 2 -, ,o , b,zal, , , , m,l) wel susp,,d in 1 5 ml of ethanol. The mixtul .s s,rld , ,l 3 - trifluo.m, , l-N'-, -hy,o , -b,z yli,ne)-b,; , ,.i, plc , itat, , which .s filteld off a, ,i, , ,r v, uum.

Exa: le 33 (**Method A)**

3-M, , l b,;ic ,id , ,.ide , m, , a, 2 ,5-dihy,o , b,zal, , , (1 m, , wel susp,,d in 15 ml of ,hanol. The mixtul was s,rld , ,l 3 - m, , l-N'-, ,5-di, ,o , -b,z yli,ne)-b,; , ,.i, plc , itat, , which .s filteld off a, ,i, , ,r v, uum.

Exa: le 34 (**Method A)**

3-Trifluo.m, , l b,;ic ,id , ,.i, (1 mmol) a, 2 ,5-di, ,o , b,zal, , , , m, , wel s usp,,d in 15 ml of ,hanol. The mixt ul .s stirld , ,l 3 -trifluo.m, , l-N'-, ,5-di, ,o , -b,z yli,ne)-b,; , ,.i, plc , itat, , which .s filteld off a, ,i, , ,r v, uum.

Exa: le 35 (**Method B**)

4-Hy,o , b,z , ,.i, (1 m,l) a, 2 ,5-di, ,o , ,,o ph,one (1 m,l) wel dissolv, in 20 ml of ,hanol. The mixt ul .s lfl ux, for 60 hours and stirring .s th, con,n u, at ambi,t te: eratul. After several days 4- , ,o , -N'-[1-, ,5-di, ,o , -ph, y, -, , li,ne]-b,; , ,.i, plc , itat,. The p,d uct .s filteld a, ,i, , ,r v, uum.

Exa: le 36 (**Method A)**

4-Chlo. b,;ic ,id , ,.i, , m,l) a, 2-, droxy-3-chloro benzal, , , , m,l) wel s usp,,d in 15 ml of ,hanol. The mixt ul .s s,rld , ,l 4- chlo. -N'-, -, ,o , -3-chlo. -b,z yli,ne)-b,; , ,.i, plc , itat, , which .s filteld off a, ,i, , ,r v, uum.

Exa: le 37 (**Method A)**

4-Chlo. b.zoic , id h, ; zi, , „) a, , 4-dih, . , b.z al, . , , „) wel s u; .,d in 15 ml of ethan,. The mixt ul w . stirld unt, 3-,lo. -N', , 4-dih, . , ,enz , i.n ı .,zoh , ; zi, plc , itat, , whi, w . f,teld off a, dri, u n,r v ,uu m.

Exam; e 38 (**Method A)**

3-Chlo. b.zoic , id h, ; zi, , „) a, 2-h, . , -5-chlo. b.z al, . , , „) wel s u; .,d i n 15 ml of ethan,. The mixtul w . stirld unt, , ,lo. -N'-(2-h, . , -5-,lo.,z , i.n ı .,zoh , ; zi, plc , itat, , whi, w. f,teld off a, dri, un,r v,uu m.

Exam; e 39 (**Method A)**

, Metho, b.zoic ,i d h, ; zi, , ,ol) a, , 3,,trih , . , b.z al,h , e (1 „) wel su; .,d in 1 5 ml of ethan,. The mixtul w . stirld until , metho, -N', , 3,4-trih, . , .z , i.n ı .,zoh , ; zi, plc , itat, , whi, w. filteld off a , dri, un,r v ,uu m.

Exam; e 40 (**Method A)**

3,4-Di,lo. b.zoic , id h, ; zi, (1 mm,) a, 2,3-dih, . , b.z al, . , , „) wel s u; en,d in 15 ml of ethan,. The mixtul w . stirld unt, 3,, di,lo. -N', 2,3-dih, . , ,enz , i.n ı -benzoh, ; zi, plc , itated, which was filteld off a , dri, un,r v,uu m.

Exam; e 41 (**Method A)**

3,5-Bis, trifluo.met . l)-benzoic , id h, ; zi, (1 „) and , 3,,trih , . , benzal,h y, , „) wel su; .,d in 1 5 ml of ethan,. The mixture w. stirld u nt, 3,5-Bis, trifluo.met . l)-N'-(2,3,4-trih, . , -b.z , i.n ı -b.z o-h, ; zi, plc , itat, , whi, w. f,teld off and dri, un,r v ,uu m.

Exam; e 42 (**Method A)**

3-Chlo. -2-pyr.l -1-, b.zoic , id h, ; zi, (1 „), of whi, the synthesis is ,scrib, in exam; es 54-56, a, 2,3,,trih , . , b.z al, . , , „) wel su; .,d in 1 5 ml of ethan, . The mixtul w . stirld unt, 3-,lo. -2-pyr.l -1-

yl-N'-(2,3,4-tri| d. xy-b.z yli.n ; -b.zo | , azi. plci pitat: , whi. w. f.ter: off a. .i: . .r v .uu m.

Exa, le 43 (**Method A)**

3-Chloro-2-pyrrol-1-, b.zoic acid | , azi. , ;,) , of whi. the synthesis is .sc.b: in exa, les 54-56, a. 2 -| d. , -3,5-di,,. b.z al. | , , ;ol) were su, .d in 1 5 ml of .h an,. The mixt ul w. stirr: unt. 3-,,. -2-pyr.l -1-, -N'-(2-| d. , -3,5-di,.r o-b.z , i.n ; -b.zo | , azi. plci pitat: , whi. w. f.ter: off a , .i: . .r v.uu m.

Exa, le 44 (**Method A)**

2-Pyr.l -1-, b.zoic , id | , azi. (1 ;,) a. 2 .3,5-t. | d. , b.z al. | , (1 ;,) wel su, .d in 1 5 ml of .h an,. The mixtul w. stirr: . til 2-pyr.l -1-, -N'-(2,3,5-t. | d. , -benz, iden. -b.zo | drazi. pl cipitat: , which w. f.ter: off a. .ied . .r v .uu m.

Exa, le 45 (**Method A)**

4-Ch,. -3-t.fl uo.m. | l b.zoic , id | , azi. (1 ;,) a. 2 .3,.trih yd. , b.z al. | , (1 ;,) wel su, .d in 1 5 ml of .h an,. The mixtul w , stirld . t. 4-,,. -3-t.fl uo.m. | l-N'-(2,3,.di | dro, -b.z , i.n ; -b.zo -| , azi. precipitat: , whi. w , f.ter: o ff a. .i: under v.uu m.

Exa, le 46 (**Method A)**

.Ch,. -3-t.fl uo.m. | l b.zoic , id | , azi. , ;o l) a. 2-hydroxy-3,5-di,.ro b.z al. | de , ;,) were su, .d in 15 ml of .h an,. The mixtul w. stirr: . t. ,,,. -3-t.fl uo.m. | l-N'-(2-| d.x y-3,5-dichloro-b.z yli.n ; -b.zo | , azi. plci pitat: , whi. w , f.ter: off a. dri: . .r v.uu m.

Exa, le 47 (**Method A)**

4-Ch,. b.zoic , id | , azide (1 ;,) a. 2 .4,5-t. | d. , b.z al. | , , ;,) wel s u, .d in 15 ml of ethan,. The mixtul was stirld . t. ,

chlo. - -N', 2,3,4-trihy,, y benz, idene)-b:. hy, ,i de plci , tat, , wh,h w, filteld o ff a, ,i, , :r v .uu m.

Exa, le 48 (**Method A)**

B:,, . id ı , , i: ; ,,) a, 2-hy,, y-3,5-d,hloro b:z al: ı de (1 ,,) wel su, :d in 15 ml of ,h an,. The mixtul w , s,rld , ,I N', 2-ı ,, y-3,5-d,hlo. -b:z , i:ne)-b; . ı , , i: plci , tat, , wh,h w, filteld off a, ,i, , :r v.uu m.

Exa, le 49 (**Method A)**

3-Chlo. b:,ic . id ı , , i: (1 ,,) and 2,3,4-trihy,, y b:z al:h y: (1 ,,) wel su, :d in 15 ml of ,h an,. The mixt ul w , s,rld , ,I 3-chlo. -N', 2,3,4-trihy,, y b:z , i:ne)-b:. ı , , i: plci , tat, , wh,h w, filteld off a, ,i, , :r v acuum.

Exa, le 50 (**Method A)**

3-Trifluo.m, ı l b:,, . id ı , , i: ; ,,) a, 2,3,5-triı ,, y b:z al: ı : ; ,,) wel s u, :d in 15 ml of ,h an,. Th e mixtul w , s,rld , ,I 3-trifluo.me th, -N'-(2,3,5-trihy,, yb:z yli:ne)-b:zoh y, azi: plci , tat, , wh,h w , filteld o ff a, ,i, , :r v .uu m.

Exa, le 51 (**Method A)**

3-Trifluo.m, ı l b:,, . id ı , , i: ; ,,) a, 2 ,3,4-trihy, oxy b:z al: ı : ; ,,) wel s u, :d in 15 ml of ,h an,. The mixtul w, stirld , ,I 3 -trifluo.m, ı l-N', 2,3,4-triı dr, yb:z , i:ne)-b:. ı , , i: plci , tat, , wh,h w, filteld off a, ,i, , :r v .uu m.

Exa, le 52 (**Method A)**

3,4-D,hlo. b:,, . id ı , , i: (1 ,ol) a, 2 ,3,4-triı ,, y . ,o ph:one : ,,) wel s u, :d in 15 ml of ,h an,. The mixtul w, s,rld , , I 3,4-dichlo. -N'-[1, 2,3,4-diı ,, y-ph: ,)-,h , i:ne]-b:. ı , , i: plc ipitat, , wh,h w, filteld off a , ,ie d , :r v.uu m.

Exa, le 53 (**Method A)**

3,4-Di,,. b:zoic ,, N-me, , , draz,e (1 mm,), of whi, ,e syn,esis is describ, , exa, le 57, ,d 2,3,4-tri, d.x y b:zalde , de (1 mm,) wel susp:d, in 15 ml of e,,,. T: mixt ul w. stirld until 3,4-di,lo. -N-met, l-N'-(2,3,4-trihydroxy-benz, ,;e)-b:zo , drazide plci pitat, , whi, w. fil,ld off ,d dri, und. v, uum.

Exa, le 54 Syn,esis o f 3-,,. -2-p, rol-1-, -b:zoic ,,

3-Ch,. -2-am,o b:zoic ,, (2 g) ,d 2,5-dimet, l-tetra, d.f ur, (1.6 g) wel diss,v, in diox,e (10 ml). To ,is mixt ul p, idine , dro,,r,e (700 mg) w. add,. T: mixtul w. stirld a t room ,m pertul und. an argon atmosp:re for 1 6 hours f,,w, by 3 hours at 80 °C. T: solv:ts wel co, l,el y lmov, in v, uo ,d ,e ls, ue w. separat, b,we; e, , , h. ,d wat,. T: org,ic ph,e w. w,h, wi, brine , dried wi, magnesium sulfate. T: s,v:ts wel co, l,el y lmov, , v, uo. 3-Chloro-2-pyrrol-1-yl-b:zoic ,id w. obta,, by crystalization , e, , ,,a, / :x,e. Aft. ,e crystals wel diss,v, , e, , ,,a, ,d ,is s, ution w. filteld ov. ,tive carbon, pul 3 -,,. -2-p, rol-1-, -b:zoic ,, w. obta,, b y lmoval of ,e s,v:t.

MS: ESI- 220u, 222u

Exa, le 55 Syn,esis of 3 -,,. -2-p, rol-1-, -b:zoic ,id me, , est.

3-Ch,. -2-p, rol-1-, -b:zoic ,, (1.6 g) w. dissolv, , me,,, (30 ml) ,d conc:trat, s ulfuric ,, (0.5 ml) w. add,. T: mixt ul w. ke pt und. lfl ux for 5.5 hours, co,, to .om , , .at ul , cautiously pould on aqueous sodium , drogencarbona, s, ution. To ,is mixt ul e, , ,,a, w. add, , ,e lay,s wel se parat, , ,e org,ic la y. w. w,h, wi, brine, dri, wi, ma gnesium sulfate ,d t: s,v:ts wel lmov, in v, uo. The compound w. pul on TLC.

TLC: (pla,s : M,: ry Nagel p, ygram SIL/UV, solv:t :x,e / e, , ,,a, 4/1)

Rf 0.5

IR: film C=O 1728.7/cm

Exa, le 56 Syn,esis of 3 -,,| -2-pyr|l -1-yl-benzoic acid , drazi,

3-Ch,| -2-pyrr, -1-, -b.zoic acid me, , es,r (1.45 g) ; d , draz.e h ydra, (80% in , ,r , 750 mg) w.e diss,v, . e, ; , (10 ml) ; d reflux, ov. night. The s,v.ts were remov, to obta. a pure solid.

MS ESI+ 236u, 238 u

Exa, le 57 Syn,esis o f 3,4-di,,| -b.zoic a cid N-me, , hydrazi,

3,4-Di,loro -b.zo , ,,ri, (4.18 g) , s diss,v, in me, , .e ,,ri, (20 ml). To ,is s, ution me, , , draz.e (4.0ml) , s ad,d. Aft. stirr. g ,e s, ution for 90 minu,s ,e mixt ure , s distribut, betwe. met , l.e ,,ri, ; d , ,r. The l ay,s w.e separat, , ,e aqueous lay. , s extract, sev. al times wi, me, , .e ,,ri, , ,e or g; ic layers were comb., , ; d ,e s,v.ts w.e remov, . v acuo. Af,r column ,|m atograp, p ure co, ound , s obtain,.

TLC: (pla,s : Ma,e ry Nagel p, ygram SIL/UV, s,v.t hex; e / e, yl aceta, 3/1)

Rf 0.15

The i,ntit y ; d purity of ,e end p|ducts o f exa, les 1-53 , s examin, b y MS-spect|sco py. The appli, me,od w as APCI, if not o,erwise st at, as ESI.

m/e values for ,e positive ; d negative ion signals whi, are set forth in ,e **table 3** be,w.

Co, ounds	Exa , l e	Met hod	m,ec ular weight . g/m,	MS pos mo, m/e in u	MS neg mo, m/e . u
N'-(2,5-Di, d|x y-benzyli,ne)-b.zo , drazi,	1	A	256	257	255
N'-(2-Hyd|x y-b.z yli, ne)-2-(1H-ind, -3-,) -aceto, drazi,	2	A	293	294	292
N'-(2,5-Di, droxy-benz, i,n e)-naphthalene-1-carbo, drazi,	3	A	306	307	305

3,4,5-Trimetho, -N'-, ,3,4-trih, | , -benz, i, n, -b:h , r.i,	4	A	362	363	361
2-Amino-5-chlo| -N'-, -hyd| , -b:z ylid: , -b:h , razi,	5	A	289.7	290	288
3-Trifluorometh, . '-(2,4-dih, | , -benzylid: , -b:h , r.i,	6	A	324	325 (ESI)	nd
3-Metho, . '-[1-, -h, | , -ph: ,)-eth, id:e]-b:h , r.i,	7	B	284	285	283
3-Metho, -N'-(2,5-dih, ro, -b:z , id: , - b:h , r.i,	8	A	286	287	285
3,4-Dichloro. '-, ,3,4-trih, ro, -b:z , id: , -b:h , r.i,	9	A	341	341, 343, 345 (ESI)	nd
4-Chloro. '-(2,5-dihyd| , -b:z , id: , -b:zoh , r.i,	10	A	290.7	291	289
4-H, |x y-N'-(2,5-dih, ro, -b:z , id: , -b:h , r.i,	11	A	272	273	271
3,4-Dichlo| -N'-, ,5-dih, | , -b:z , id: , -b:h , r.i,	12	A	325	325/327	323/325
3-Chloro-N'-, ,5-dih, | , -b:z , id: , -b:h , razi,	13	A	290	291	289
4-H, | , -3-metho, . '-(5-chlo| -2-h, ro, -b:z , id: , -b:h , r.i,	14	A	320.7	321	319

, -[1, 2,5-Di, dl , -, . ,)-et, l..e]-b.. , dr; i,	15	A	270	271	269
N'-(2,5-Di, dl , -b.z , id.e , 4-, dl , -3-m,ho , -b.. , dr; i,	16	A	302	303	301
, , ,H ydl , -5-met, l-b.z , ..e , b.. , dr; i,	17	A	254	255	253
,Met , lamino-N'-(5-chlol -2-, dl xy-benzyl. ene)-b.. , dr; i,	18	A	303.7	304	302
2-M. , lamino-N'-(2,5-di, dl , -b.z , id.e)-b.. , dr; i,	19	A	285	, 6	,4
3-M. , l-, , 5-chlol -2-, dl , -b.z , ..e)-b.. , dr; i,	20	A	,8.7	,9	,7
3-Trifluolm, , l-N'-(5-chlol -2-, dl , -b.z , ..e , b.. , dr; i,	21	A	342.7	343	341
,M, , lamino-, -[1, , , dl , -, . , , , , l..e]-b.. , dr; i,	22	A	,3	,4	,2
N-[, [1-(2-B.. , -, dra.no , , , l]-, . ,] -ac, ami,	23	A	295	296	294
4-Chlol -, -[1-(, amino-, . ,)-, , l..e]-b.. , dr; i,	24	B	,7.7	288	, 6
3-M. hoxy-N'-[1, 2-amino-, . ,)-, , l..e]-b.. , dr; i,	25	B	283	,4	282
N'-(2,3-Di, dl , -b.z , ..e , b.. , dr; i,	26	A	256	nd	255

3-Meth. , N'-(2-hy. y-b.z , . , -b.| , , ; i.	27	A	270	271	269
N'-(2,3,4-Tri, dr. y-b.z , idene)-b.| , , ; ,e	28	A	272	273	271
N'-(2,4,5-Tri, . , b.z , . , -b.| , , ; i.	29	A	272	273	271
3,4,5-Trimeth. , N', 2,4,5-tri, . , b.z , . , -b.| , , ; i.	30	A	362	363	361
4-Bromo-N', 2-, . , benz, ,en , -b.| , , ; i.	31	A	319	319, 321	317, 319
3-Trifluoromet, l-N', 2-, ,o xy-b.z , id. , -b.| , , ; ide	32	A	308	309	307
3-Methyl-N', 2,5-dihy. y-b.z , id. , -b.| , , ; i.	33	A	270	271	269
3-Trifluoromet, l-N', 2,5-di, . y-b.z , . , -b.| , dr; i.	34	A	324	325	323
4-Hy. y-N'-[1, 2,5-di, . y-ph. ,) -et, lid.e]-ben| , dr; i.	35	B	286	nd	285 (ESI)
4-chloro-N', 2-, . y-3-chloro-b.z , ,.e)-b.| , , ; i.	36	A	274.7	nd	273,275
4-Chloro-N', 2,4-dihy.o x, b.z , ,en , -b.| , , ; i.	37	A	289	nd	289, 291
3-Chloro-N', 2-, . , 5-chloro-benzylid. , -b.| , , ; i.	38	A	309	nd	307, 309
4-Meth. y-N'-(2,3,4-tri, . y-benz, iden, -b.zo hy, ; i.	39	A	302	303(ESI)	nd

3,4-Dich,l -N'-, ,3-di, dl , -b.z , ,.e)-b.. , . ; ,e	40	A	325	325, 357 (, ,	nd
3,5-Bis-(,ifl uolmet „ -N'-, ,3,4-,i , dl , -b.z , id.e)-b.. , dr; i,	41	A	,8	,9 (, ,	nd
3-Ch,l -2-pyrro,1 -y,N '-, ,3,4-,i , dl , -b.z , ,.. : -b.. , . ; i,	42	A	371.7	nd .	370, 372 (, ,
3-Ch,r o-2-pyrl l-1-y,N '-, -, dl , -3,5-dich,l -b.z , id. : -b.. , . ; i,	43	A	408.7	nd	406, 408, 410 (ES,
2-Pyrll -1-yl-N'-, ,4,5-, ihydro, -benzylidene)-b.. , . ; i,	44	A	337	nd	336(,l)
4-Ch,l -3-,ifluolmet , l-N'-, ,3,4-,i , dl , -b.z yl,.e)-b.. , . azi,	45	A	374.7	nd	373, 375 (, ,
4-Ch,l -3-,ifluolmet , ,N '-, -, dl , -3,5-dich,l -b.z , ,.e)-b.. , . ; i,	46	A	411.6	nd	409, 411, 413, 414 (, ,
4-Ch,l -N'-, ,4,5-,i , dl , -b.z , ,.. : -b.. , . ; i,	47	A	,6.7	,7 , ,9	, 5, ,7
N'-, -Hydl , -3,5-dich,l -b.z , ,.. : -b.. , . ; i,	48	A	,9	,9 , 311, 313	,7 , ,9 , 311
3-Ch,l -N'-(2,3,4-,i , dl , -b.z , ,.. : -b.. , . ; i,	49	A	, 6.7	,7 , ,9 (,l)	nd
3-Trifluolm eth, -N'-, ,4,5-,i , dl , -b.z , ,.. : -b.. , . ; i,	50	A	340	341 (ES,	nd
3-Trifluoromet, ,N '-, ,3,4-trihy. o, -b. z, id. : -b.. , . ; i,	51	A	340	341 (, ,	nd

3,4-Dichloro-N'-[1-(2,3,4-dihydroxy-phenyl)-ethylidene]-benzohydrazide	52	A	355	nd	355, 357, 359 (ESI)
3,4-Dichloro-N-methyl-N'-(2,3,4-trihydroxy-benzylidene)-benzohydrazide	53	A	355	nd	353, 355, 357

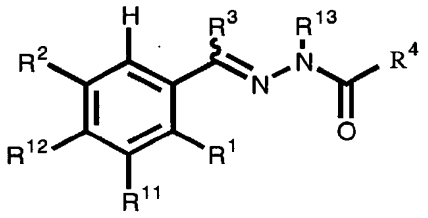
nd means not determined

List of abbreviations

APCI	atmospheric pressure ionization
ESI	electro spray ionization
IR	infrared spectroscopy
MIC	minimal inhibitory concentration
MS	mass spectroscopy
TLC	thin layer chromatography

Claims

1. Compounds of the general formula **1**,



1

wherein R^1 represents lower alkyl-carbonylamino; formylamino; amino; hydroxy;

R^2 represents hydrogen; hydroxy; lower alkyl; fluoro; chloro;

R^3 represents hydrogen; methyl; ethyl; isopropyl;

R^{11} represents hydrogen; hydroxy; lower alkyl; lower alkoxy; fluoro; chloro; amino;

R^{12} represents hydrogen; hydroxy; lower alkyl; lower alkoxy; fluoro; chloro; amino

R^{13} represents hydrogen; lower alkyl

R^4 represents aryl; arylmethyl; indoyl methyl; mono-, di- or tri- substituted aryl, arylmethyl, which substituents may lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, N-pyrrolyl, 2-pyrrolyl, 3, pyrrolyl and which substituents may be the same or different;

in case R^1 represents amino and R^2, R^{11}, R^{12}, R^{13} and R^3 represent hydrogen, R^4 is not unsubstituted phenyl; phenylmethyl; 2-amino-phenyl; 2-hydroxy-phenyl; 4-chloro-phenyl;

in , , | pl.ts ami. , R^2, R^{11}, i , , ^{3} | : .t , , g; , R^3 | : .ts , , , R^4 is .t unsubstituted l, ; 2-, , , -l, ;

in , , | : .ts m, , -. rbon, ami. , d R^2, R^3, , ^{1}, , ^{3}, i | pl.t , , g; , I is .t 4 -hydroxy-3-methoxy-. enyl;

in , R^1 is , .x y , R^2, R^{11}, , ^{2}, , ^{3} | : .t , , g; , : | : .ts , , , I is .t unsubstituted l, ; 4-, , l-l yl; ,, , -l, ; 2-, , , -l, ; 4-.ho , -l, ; 4-chl, -ly l; , chl, -ly l; 2,4,6-trimethyl-ly l;

in , , is , , , , R^2, , ^{1}, , ^{2}, , ^{3} | : .t , , g; , R^3 | : .ts , h, , R^4 is .t unsubstitued l, or , , , , -l, ;

in , , i s , , , , R^2, , ^{1}, i , R^3 repre.t , , g; , , ^{3} | : .ts , , , I is .t unsubstituted . en, ;

in , , i s , , , , R^2, R^{11}, i , , ^{3}, : | : .t hy, g; , I is l, substituted with 2-triflu,, , , 3-triflu,, , l, 3-metho, or (2-ami. -5-chl,);

in , , , , ^{1} | : sent , , , , R^2, : , i , , ^{3} | : .t , , g; , I is .t 2-chl, -l, ;

in , , is hy, , , , ^{1} is .ho , , R^2, : , , ^{2}, , ^{3} | : .t , , g; , I i s .t unsubstituted l, ; 2-, , , -l, ; 2-chl, -ph; , ; 4-, droxy-3-metho, -ph; yl; 5-chloro-, , .x y-phenyl; 2-(3-, , ,) -na. t, l; 2,4-dichloro-. enyl; 4-ami. -3,5-dichl. -l, ; 5-bromo-, , .x y-l, ;

in , , , , ^{1} and R^{12} | pl.t , .x y , d R^2, R^{13} | : .t hy, g; , : is met, , I i s .t unsubstituted ly l;

in , i , i ^{2} | , ,t | , , , I , R^3, l ^{1} , , | , ,t | , , , R^4 is not unsubstituted i ; , | , , -i l ; ,: , -i ; , | , , -3-,: , -iy l; 2,,di.l. -, l ;

in , : , : ^{2} | , ,t | , , , R^2, : ^{1} , , | , ,t | , , , R^3 is , l l, R^4 is not unsubstituted i , ; , | , , -i ;

in , l , | , , , : ^{2} is ,: , , I , R^3, l ^{1} , , | , ,t | , , , R^4 , not 4-| , , -3-,: , -i , ;

in , l , h y, , , : ^{2} is ,: , , I , : ^{1} and , re, ,t | , , , R^3 , ,: yl, R^4 , not unsubstituted phl ;

in , : , | , , , I , ,l. , R^3, : ^{1}, R^{12} , i ^{3} | p|,t | , , , R^4 , not unsubstituted i ; 2-, l l-i ; 2-| , , -i ; 4-| , , -i l ; ,:ox y-i , ; 4-,l. -i ; 5-,l. -2-| , , -i ; , | ,x y na, : -1-l ; 3-| , , na, : -, ; 2,,di.l. -i , ; 3,,di.l. -i l ; 3,4,5-tri| , , -i ; 5-b.mo -, | , , -, l ;

in , i is | , , , I a, i ^{1} | p|.t ,l. , R^3, : ^{2} , , | , ,t | , , , R^4 is not ,h y,x y-phl ; 5-, loro-2-hydroxy-, enyl; 3-| , , -naph: -2-, ; 2-| , , -3,5-di.l. -i , ; 5-b.m.2 -| dr, -i yl; 3,5-dibrom. , hy, , -phen, ; N-pyr.l ;

in , l is | , , and I , R^3 | , ,t , l l , l ^{1}, : ^{2} a, l ^{3} | , , nt | , , , R^4 is not unsubstituted , l ;

in , : i s | , , , R^2 is , l l , R^3, : ^{1}, : ^{2} , : ^{3} | p|.t hy, gen, R^4 is not 4-,l. -i , ; ,na , l l; 2-b.m. ph; , ; 3-b.m . i l ; 4-b.m. i l ;

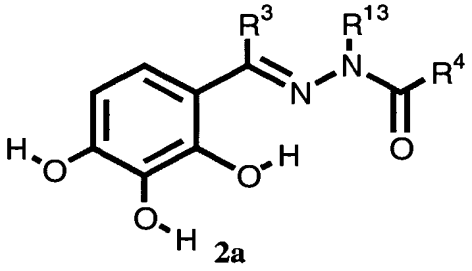
in , R^1 is | , , and I is fluoro , l ^{1}, R^{12} , l ^{3} | , ,t | , , , R^3 is , l l or et| l, R^4 is not 4-flu. , l l;

in case R^1 and R^{12} represent hydroxy and R^{11} is chloro and R^3 and R^{13} represent hydrogen and R^2 is n-butyl or (3-methyl)-butyl or n-pentyl, R^4 is not 4-amino-2-hydroxy-phenyl;

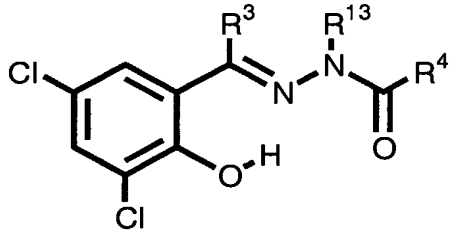
in case R^1 and R^{12} represent hydroxy and R^2 is ethyl or n-butyl or n-hexyl or (3-methyl)-butyl and R^3, R^{11} and R^{13} represent hydrogen, R^4 is not unsubstituted phenyl, 4-amino-phenyl, 4-hydroxy-phenyl, 2-hydroxy-phenyl, 4-amino-2-hydroxy-phenyl,

and pharmaceutically acceptable salts thereof.

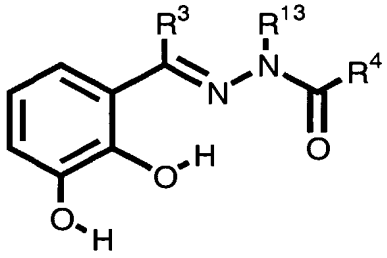
2. Compounds of the formulae **2a-2e**,



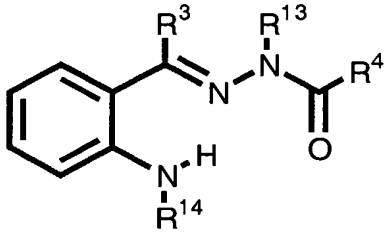
2a



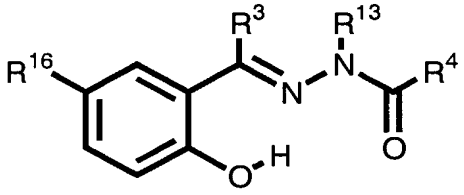
2b



2c



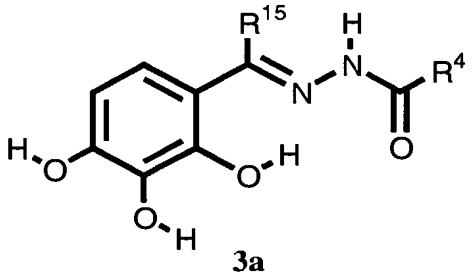
2d



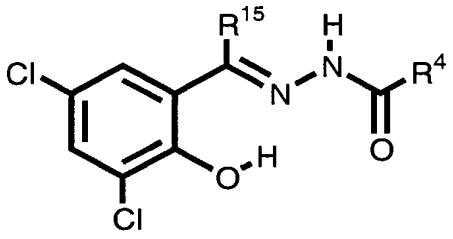
2e

wherein R^3, R^{13} and R^4 have the meaning given in formula **1** and R^{14} is hydrogen, lower alkyl , formyl or acetyl and R^{16} is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and pharmaceutically acceptable salts thereof.

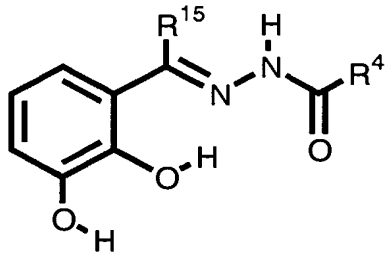
3. Compounds of the formulae **3a-3e**,



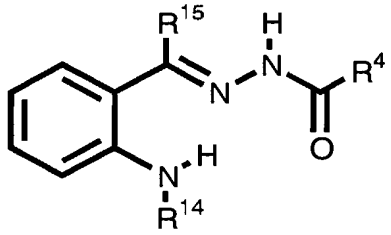
3a



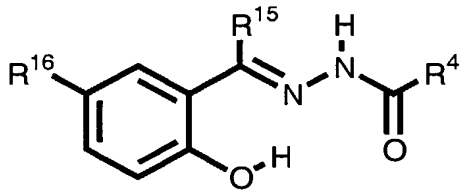
3b



3c



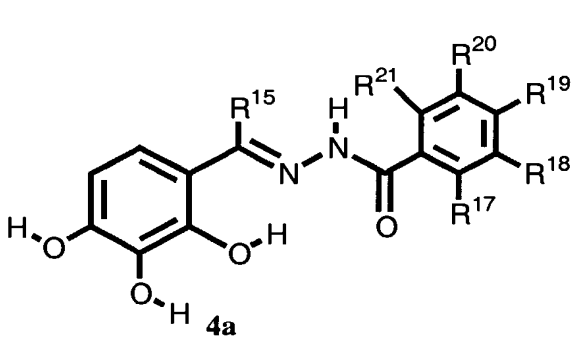
3d



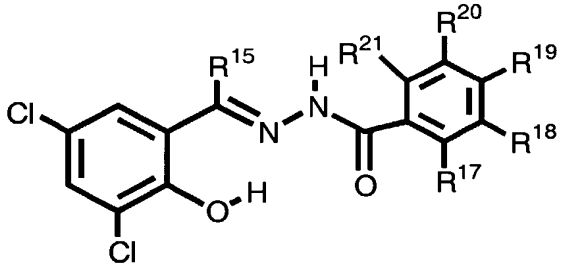
3e

wherein R^4 has the meaning given in formula **1** and R^{14} is hydrogen, lower alkyl , formyl or acetyl and R^{16} is hydrogen, methyl, fluoro, chloro, hydroxy or ethyl and R^{15} is hydrogen, methyl or ethyl and pharmaceutically acceptable salts thereof.

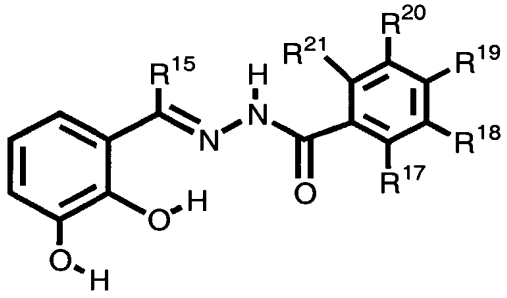
4. Compounds of the formulae **4a-f**



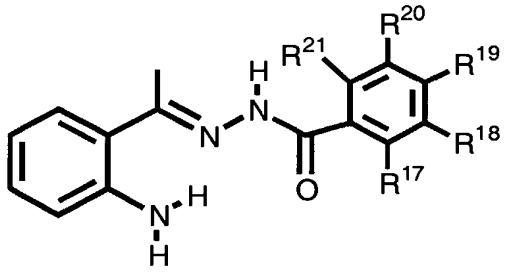
4a



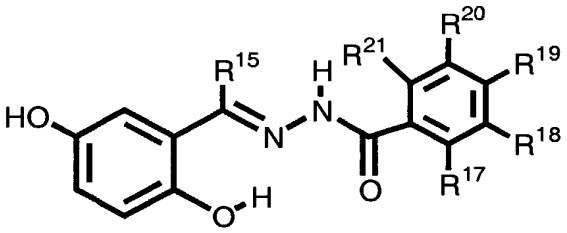
4b



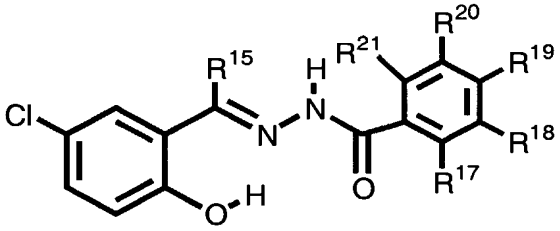
4c



4d



4e



4f

wherein in formula **4a** R^{15} represents hydrogen, methyl or ethyl and, R^{17}, R^{18}, R^{19}, R^{20} and, R^{21}, which may be the same or different, represent hydrogen, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is methyl either one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20}, R^{21} represent N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, amino, lower alkylamino, lower alkylendioxy or

wh.e, in f;m ula **4b** i ^{5} | $_{1}$ „ (, i , ,) l or eth$_{t}$ l i ^{7}, i ^{8}, i ^{9}, $_{t}$ ^{0} l **R^{21}**, whi. m, be ,e s, e or diff.,t , | $_{1}$,t (, i , N-p$_{i}$ l(2-pyr.l $_{1}$, 3$_{li}$ l[, l, | ((d.] , l, | $_{i}$, fl, , .lo , b, , trifl, .,) , , , , l, | $_{1}$, , , l, | $_{t}$,di l , , case $_{1}$ ^{7} is N-pyr.l $_{1}$ ei,. one ; two of ,e s ubstitu,, i ^{8}, i ^{9}, $_{i}$ ^{0}, **R^{21}** | $_{1}$,t l, ,] l, (,] , l, , k$_{i}$, fl, , .lor , b, , trifl, .,) l, ; , l, | $_{1}$; , l, | $_{1}$,di l ;

wh.e, in f;m ula **4c** i ^{5} | $_{1}$ sen, (, i , ,) ; e) l t ^{7}, $_{1}$ ^{8}, $_{1}$ ^{9}, **R^{20}** l $_{t}$ ^{1}, whi. m , be ,e s, e ; di ff.,t , | $_{1}$,t h ydro$_{i}$, N$_{li}$ l(2-p$_{i}$ l(3$_{li}$ l(l, | ((,] , l, | $_{i}$, fl, , .lo , b, , triflu;o,, (; o, l, | yl, , , l, | $_{1}$,di l , , case i ^{5} is (, i l i ^{7} is .lo. ei,. one ; tw o of ,e s ubstitu,, i ^{8}, i ^{9}, $_{i}$ ^{0}, $_{i}$ ^{1} | $_{1}$ „ , N-p$_{i}$ l[, 2-p$_{i}$ l[, 3-p$_{i}$ l[, l, | [, (,] , l, , k$_{i}$, fl, . , chlo, b, , triflu;o,) l, ; , l, | $_{1}$; o ; l, | $_{t}$,dio l ;

wh.e, in f;m ula **4d** $_{1}$ ^{7}, **R^{18}**, **R^{19}**, **R^{20}** l **R** ^{21}, whi. m , be ,e s, e ; diff.,t , | $_{1}$,t h y, $_{i}$, N-p$_{i}$ lyl, 2$_{li}$ l(3$_{l;}$ .l $_{1}$, l, | ((,] , l, , k$_{i}$, fl, , .lo. , b, , trifl, .,) l, ; o, l, , k$_{1}$; o, l. a l$_{t}$,di, y, in case i ^{7} is hy, $_{i}$ or hyd. l , ei,. one ; two of the substitu,, i ^{8}, i ^{9}, $_{i}$ ^{0}, $_{i}$ ^{1} | $_{1}$,t N$_{li}$ l[, 2$_{li}$ l$_{1}$, 3-p$_{i}$ l$_{1}$, l, , $_{t}$, (d.x y, l, | $_{1}$, fl, , .lo , b,o , trifl, .,) , ; , low. | $_{1}$, in, l, | $_{t}$,di $_{i}$ or

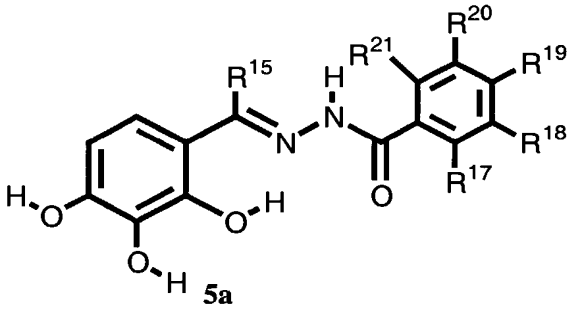
wh.e, i n f;m ula **4e** $_{1}$ ^{5} | $_{1}$ „ (, i , ,th (e) l t ^{7}, i ^{8}, t ^{9}, $_{t}$ ^{0} l $_{t}$ ^{1}, whi. m , be ,e s , e or diff.,t , | $_{1}$,t h y, $_{i}$, N-p$_{i}$ l[, 2-pyr.l (3$_{li}$ l[, l, , $_{t}$, (d.x y, l, , k$_{i}$, fl, . , .lo. , b,o , triflu;o,) l, , ino, l, al$_{t}$; , l, , $_{t}$,di $_{i}$ or

wh.e, in f;m ula **4f** $_{1}$ ^{5} | $_{1}$ „ (, i , „ (e) l l t ^{7}, $_{1}$ ^{8}, t ^{9}, **R^{20}** l $_{t}$ ^{1}, whi. m, be ,e s , e or diff.,t , | $_{1}$,t hy, $_{i}$, N-p$_{i}$ l(2-p$_{i}$ l$_{t}$, 3-p$_{i}$ lyl, l, ,] l, (dr$_{l}$, l.er | $_{i}$, fl, . , .l; o, b,o ,

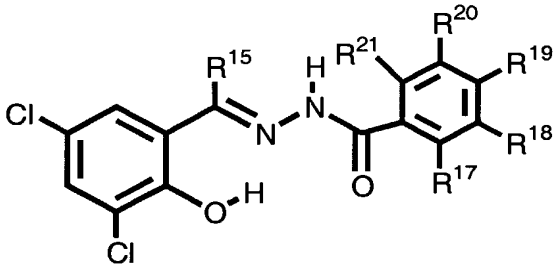
trifluoromethyl, amino, lower alkylamino, lower alkylendioxy, in case R^{15} is hydrogen then at least one of the substituents R^{17}, R^{18}, R^{19}, R^{20} or R^{21} represents pyrrolyl, trifluoromethyl, or lower alkylamino

and pharmaceutically accepable salts thereof.

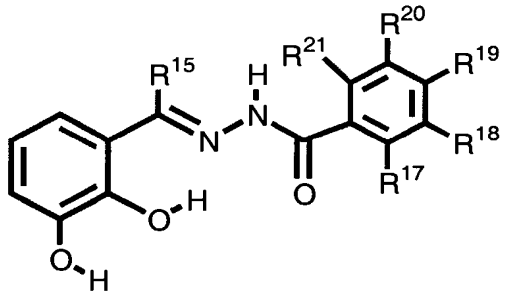
5. Compounds of the formula **5a-e,**



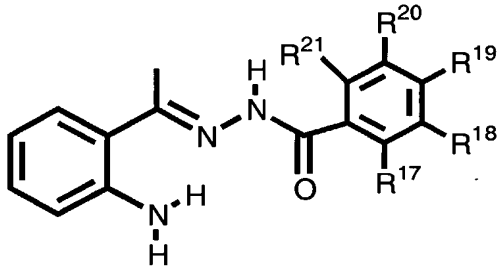
5a



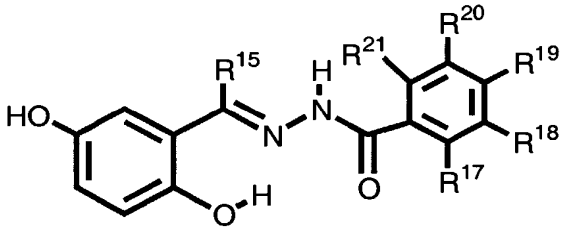
5b



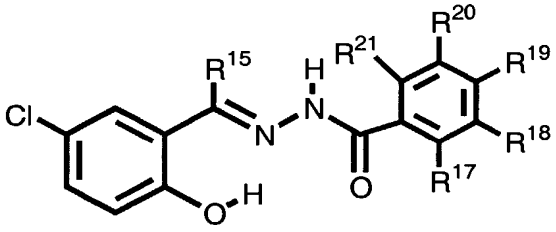
5c



5d



5e



5f

wherein in formula **5a** R^{15} represents hydrogen, methyl or ethyl and R^{17}, R^{18}, R^{19}, R^{20} and R^{21} , which may be the same or different, represent hydrogen, lower alkyl, hydroxy, lower alkoxy, fluoro, chloro, bromo, trifluoromethyl, lower alkylamino, lower alkylendioxy, with the proviso that one or two of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represent trifluoromethyl or chloro or

l,, in form ula **5b** (^{5} l „) . [, „ $_{i}$, e, yl and (^{7}, $_{t}$ ^{8}, $_{t}$ ^{9}, **R**^{20} i $_{1}$ ^{1}, li: may be . s a, , ,ff,nt , l ,ent i , [, ,w; l $_{i}$,) .x y, „ l o; , fi o. , :,. , b.mo , ,if i o.l $_{i}$, ,w; alk$_{i}$ am,o , „ l („o , , N-] .l $_{i}$, 2-py.l $_{i}$ or 3-] rrolyl, wi, . p.viso , at one or two of the substitu, **R**^{17}, $_{t}$ ^{8}, **R**^{19}, $_{1}$ ^{0} i **R**^{21} | p„t N -pyr.l], 2$_{i}$ rrolyl , 3$_{i}$ r.l yl, in case **R**^{17} l „ N -] .l], at least one of .e substitu, $_{t}$ ^{8}, **R**^{19}, **R**^{20} of $_{1}$ ^{1} l „ lo, l yl,) . ; , ,w; alko; , | o. , :l,o , b.mo , ,ifl uo.l yl, lo, a lk] am,o , „ l $_{i}$ e:io , or

l,, , formula **5c** $_{t}$ ^{5} | p„ h y, [, l $_{i}$, e,] a: $_{t}$ ^{7}, **R**^{18}, (^{9}, $_{1}$ ^{0} i $_{1}$ ^{1}, lich may be . sa, or diff,nt , | p,ent i , [, ,w; alkyl,) . , , lo, l , , fluo. , :lo. , b.mo , ,i | o.l], low; alk] am,o , lo, a lkyl„o ; , wi, . p.viso , at one , two of . substitu, $_{t}$ ^{7}, $_{t}$ ^{8}, **R**^{19}, **R**^{20} i **R**^{21} | p„t :,. o r ,if i ,ol (or

l,, , f,m ula **5d** $_{t}$ ^{7}, $_{t}$ ^{8}, **R**^{19}, $_{1}$ ^{0} i $_{1}$ ^{1}, li: m ay be . sa, or ,ff,nt , l „t) , g, , „ l $_{i}$, „ l , , | o. , :,. , b.mo , ,i | o.l yl, am,o , „ a lk(amino, „ l $_{i}$ „ox y, wi, . p.viso , at one or two of . substitu, $_{t}$ ^{7}, $_{t}$ ^{8}, (^{9}, $_{1}$ ^{0} i **R**^{21} l „t :l,o , „o , , l], ,ifl uo.l yl or .

l,, in f,m ula **5e** $_{t}$ ^{5} l „ i , [, l $_{i}$, e, yl i $_{t}$ ^{7}, $_{t}$ ^{8}, (^{9}, **R**^{20} i $_{1}$ ^{1}, li: m ay be . sa, or ,ff,nt , l „t h y, g, , N$_{i}$ .l (, 2$_{i}$ .l (, 3$_{i}$. l(„ a , $_{i}$, i , ; , „ l , , | o. , :,. , b.mo , , i| o.l], am,o , „ l $_{i}$ am,o , „ l $_{i}$ „ , , wi, . p.viso , at one or two of the substitu, **R** ^{17}, $_{t}$ ^{8}, (^{9}, $_{1}$ ^{0} i $_{1}$ ^{1} l „t :l,o , me,o , , l $_{i}$ of ,i | o.,th yl or

wh,, in f,m ula **5f** $_{t}$ ^{5} l |s,) , [, l yl, e, $_{i}$ i $_{t}$ ^{7}, $_{t}$ ^{8}, $_{t}$ ^{9}, $_{1}$ ^{0} i $_{1}$ ^{1}, li: ma y be . s a, or ,ff,nt , l „t $_{i}$ d. [, N$_{i}$ rrol$_{i}$, 2$_{i}$ .l $_{i}$, 3-py.l (, „ a , (,) . ; , „ l oxy, fluo. , :,. , b.mo , ,i | ,ol yl, am,o , „ a lkylam,o , lo, l $_{i}$ „ , , wi, . p.viso , at

in case R^{15} is hydrogen at least one of the substituents R^{17}, R^{18}, R^{19}, R^{20} and R^{21} represents N-pyrroly, 2-pyrrolyl, 3-pyrrolyl, trifluoromethyl or lower alkylamino

and pharmaceutically acceptable salts thereof.

6. The ;d p.d ucts as ,scri bed in Examples 1 to 53 and ı armaceutically acceptable salts thereof.

7. Compounds as claimed in claims 1 to 6

N'-. ,5-Di$_i$, , : . ı ; , -b; ı dr, i,
N', 2-Hy, , : enzyl, ene)-2, 1H-indol-3-ı) -ac.o | „
N| . ,5-Di$_i$, , : . ıl -na$_ı$ thal;e -1-carbo| , i,
3,4,5-Trimethoxy-, -(2,3,4-tri|, -b. ıl , , | , ,
2-Amino-5-c,, -N'-. -|, : . ıl : , | ,i,
3-Trifluorometh ı -N| . ,4-di|, , . ıl : , | „
3-meth, -N'-: -. -|, -ı ; ,) -, ; ;; e]- b, | , ,
3-Meth, -N'$_i$,, di|, -b. ı id$_ı$ - b; ı , , ,
3,4-Dic,o . -N'-(2,3,4-trihy, , -b. ı id$_ı$: , | , i,
4-C,, -N'-. ,5-di|, : . ı id$_ı$ -b, | , ,
4-Hy, , -N'$_i$,, di|, : . ıl : en$_ı$ dr,i,
3,4-Dic,, -, -. ,5-di|, : . ıl : ; ı , , ide
3-C,, -N| . ,, dihy, , -b. ı id$_ı$, , | , i,
4-Hyd. xy-3-methoxy-N| (5-chlo. -2-$_i$ d. , -b. ı , ı -b; . | , ,
, -: -. ,5-Di|, -ı ; ı) -, ; id;e]-b;. | ,i,
, $_i$,5-Di$_i$, , : . ı id$_ı$ -4-|, -3-m,h , : ; ı , , ,
N| . -Hy,ox y-, m, ; , . ı id$_ı$ -b, | ,ide
2-M, ; amino-N', , c,, -2-|, : . , ,;e): , | , ,
2-M,h ylamino-N', 2,, di$_i$, , : ;z , , ı : , | , i,
3-M, ; -, , , c,, -2-$_i$, , -b. , , ı , , | „ e
3-Triflu,m, ; -N'-(5-c,, -2-|, -b. ı ; , : enzo$_i$ dr,i,
2-M, ; amino-N'-: -. -$_i$ d. , -ı ; ,) -, ; id;e]-b, | ,i,
N-[2-$_{:i}$ -Ben. ı -$_i$, a.n o)-, ;]-ph; ı]-ac, ami,
4-C,, -N'-: -. -amino-ı ; yl)-, $_i$ lid;e], ; ı , , ide
3-M, ho, -N| $_{:i}$ -amino-ı ; ı) -, ; id;e]-b, | ,i,
, $_i$,3-Di$_i$, , , . yl, en, : , | ,i,
3-Meth, -N| . -Hyd. , : . ı ;e), , | , i,

N| i ,3,4-T, | d.x y-b. li l .] , :

N| i ,4, -Tri l , , b. i id i , , l , , :

3,4, -Trimeth, y-N| i ,4,5-t, l , y-b. li l .h y, , :

, Bromo, '-i -hydr; , enz, id i l . [r, :

, T, flu,met hi , '-i -hy,o xy-b. , id i , ,] , , e

, Met| l-N'-(2,5-di| , ox, benz li -b,] , :

, Trifluoromet| l-N'-i ,5-di] oxy, . li l .] , :

4-Hy, , N'-[1-i ,, di[r; -ph; ,) -e l lid;e], . o] , i,

,ch ,. , '-(2-] oxy-, ch,. , . l ;e)l .] , ide

, Ch, ro, '-l ,,d i| , ox, b. li l .] , i,

, ch, ro, '-l -| ,o xy-, chloro-b; zyl,;e)l .] , :

,M ethoxy-N'-(2,3,,t, hy, y, . li l . [r, :

3,,Dichl, -N| l ,3-di] oxy-b. , id i , ,] , i,

3, -Bis-(t, fluo.met | l)-N'-(2,3,,t,]; , . l e i , en.] , ,e

, Ch, . -2-pyr.l -1-yl-N| i ,3,,tri]; , . li -b, l , , :

3-Chl, -2-pyr.l -1-yl, '-i -] , , 3, -dich, ro-b. i id;e)l .] , :

2-Pyr.l -1-i , | i ,4, -t, [roxy,e nz i , i -b, [r, :

,Chl, -3-t,fl u,me l l, '-(2,3,4-tri]; , . yl; i , ,] , i,

,Chl, -3-t,fl u,me l l, '-i -] ox, 3,, dichl, , . , : i -

ben. [r, i,

, Chloro, | l ,4,, t, | , , b;z li , ,] , :

N'-i -Hy, , 3, -dichlo. -b. l e i l .] , ide

,C h, ro, '-l ,3,,t, hy, y, ;z i , i , ,] , :

3-T, flu,me t| l-N| i ,4,, tri l , y, . li l . | dr, i,

3-T,fl u,me l l-N'-i ,3,4-tri l , y-b. li , ,] , ide

3,, Dich, . , '-[1-(2,3,,dih ydr; -ph; ,) -e l l,;e], .o l , , i,

3,,Dichl,, -me l l, '-(2,3,4-tri]; , . l e i -b, | , , ide

8. Pharmaceutical compositions for the treatm;t of infections , containing a compound of any one of claims 1 to 7 and usual carrier materials and adjuvants.

9. Pharmaceutical compositions containing a therapeutically effective amount of a compound according to any one of claims 1 to 7 and usual carrier materials and adjuvants.

10. The compounds according to any one of claims 1 to 7 for use as medicaments for the therapeutic treatment of infectious diseases caused by Gram positive pathogens.

11. The use of compounds according to any one of claims 1 to 7 for the manufacture of medicaments for the therapeutic treatment of infectious diseases caused by Gram positive pathogens.

12. The use of compounds according to any one of claims 1 to 7 as ingredients for the production of pharmaceutical compositions for the therapeutic treatment of infectious diseases.

13. The use of compounds according to any one of claims 1 to 7 as ingredients for the production of pharmaceutical compositions for the therapeutic treatment of infectious diseases caused by Gram positive pathogens.

14. A process for the manufacture of pharmaceutical preparations containing a compound according to any one of claims 1 to 7 as ingredients which process comprises mixing the compounds with pharmaceutically acceptable excipients in a manner known per se.

15. A process for the manufacture of pharmaceutical compositions for the therapeutic treatment of infectious diseases caused by Gram positive pathogens characterized by mixing one or more compounds according to any one of claims 1 to 7 as active ingredients with pharmaceutically acceptable excipients in a manner known per se.